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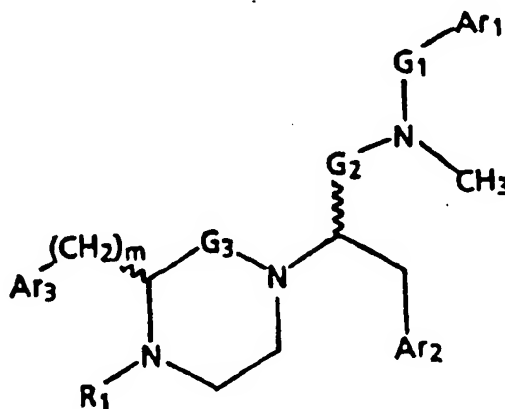
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(21) International Application Number: PCT/US96/02568 (22) International Filing Date: 11 March 1996 (11.03.96) (30) Priority Data: 08/421,719          13 April 1995 (13.04.95)          US (71) Applicant: HOECHST MARION ROUSSEL, INC. [US/US]; 2110 East Galbraith Road, P.O. Box 156300, Cincinnati, OH 45215-6300 (US). (72) Inventors: BURKHOLDER, Timothy, P.; 320 Gregorian Drive, Fairfield, OH 45014 (US). LE, Tieu-Binh; Apartment 18, 10 E. Lakeshore Drive, Cincinnati, OH 45237 (US). KUDLACZ, Elizabeth, M.; 10856 Lake Thames, Cincinnati, OH 45242 (US). (74) Agent: STEMERICK, David, M.; Hoechst Marion Roussel, Inc., 2110 East Galbraith Road, P.O. Box 156300, Cincin- nati, OH 45215-6300 (US).		(81) Designated States: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).  Published With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.	

(54) Title: NOVEL SUBSTITUTED PIPERAZINE DERIVATIVES HAVING TACHYKININ RECEPTOR ANTAGONISTS ACTIVITY

(57) Abstract

The present invention relates to substituted piperazine derivatives (herein referred to as compounds or compounds of formula (1), or stereoisomers, or pharmaceutically acceptable salts thereof and their use as tachykinin receptor antagonists. Such antagonists are useful in the treatment of tachykinin-mediated diseases and conditions disclosed herein including: asthma, cough, and bronchitis.



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-1-

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NOVEL SUBSTITUTED PIPERAZINE DERIVATIVES HAVING TACHYKININ RECEPTOR  
ANTAGONISTS ACTIVITY

The present invention relates to substituted piperazine derivatives (herein referred to as compounds or compounds of formula (1)) or stereoisomers, or pharmaceutically  
15 acceptable salts thereof and their use as tachykinin receptor antagonists. Such antagonists are useful in the treatment of tachykinin-mediated diseases and conditions disclosed herein including: asthma, cough, and bronchitis.

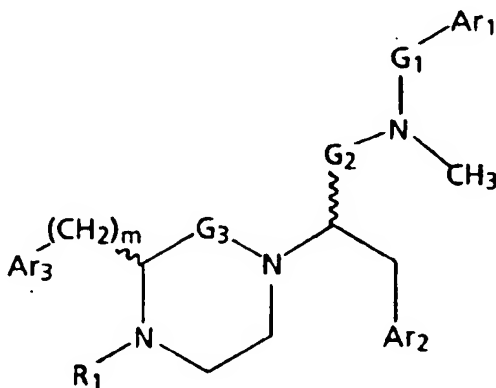
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SUMMARY OF THE INVENTION

The present invention relates to compounds of formula  
(1):

25

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formula (1)

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wherein

G<sub>1</sub> is -CH<sub>2</sub>- or -C(O)-;

-2-

$G_2$  is  $-\text{CH}_2-$  or  $-\text{C}(\text{O})-$ ;

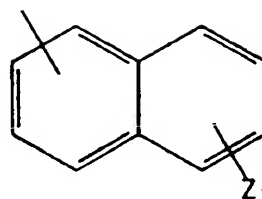
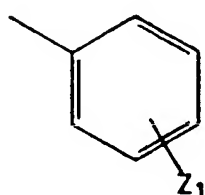
$G_3$  is  $-\text{CH}_2-$  or  $-\text{C}(\text{O})-$ ;

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$m$  is 0 or 1;

$\text{Ar}_1$  is a radical chosen from the group:

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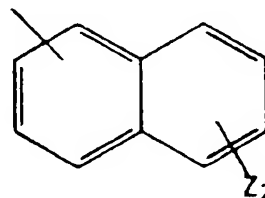
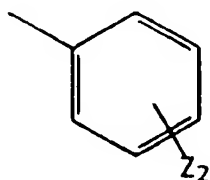
wherein

$Z_1$  is from 1 to 3 substituents each independently chosen from the group consisting of hydrogen, halogen, benzyloxy, hydroxy,  $\text{CF}_3$ ,  $\text{C}_1$ - $\text{C}_4$  alkyl, and  $\text{C}_1$ - $\text{C}_4$  alkoxy;

20

$\text{Ar}_2$  is a radical chosen from the group

25



30

wherein

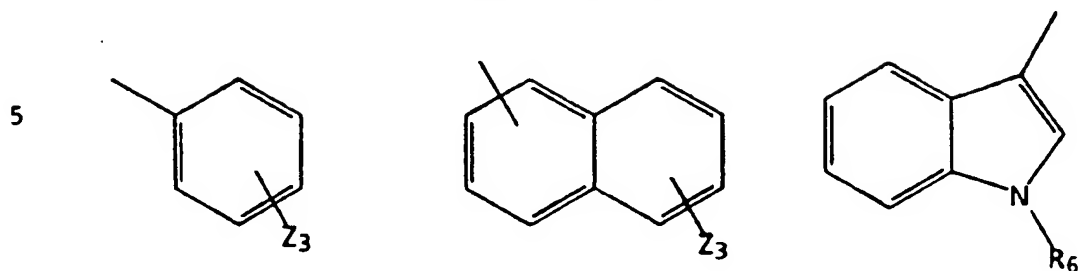
$Z_2$  is from 1 to 3 substituents each independently chosen from the group consisting of hydrogen, halogen, benzyloxy, hydroxy,  $\text{CF}_3$ ,  $\text{C}_1$ - $\text{C}_4$  alkyl, and  $\text{C}_1$ - $\text{C}_4$  alkoxy;

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-3-

Ar<sub>3</sub> is a radical chosen from the group

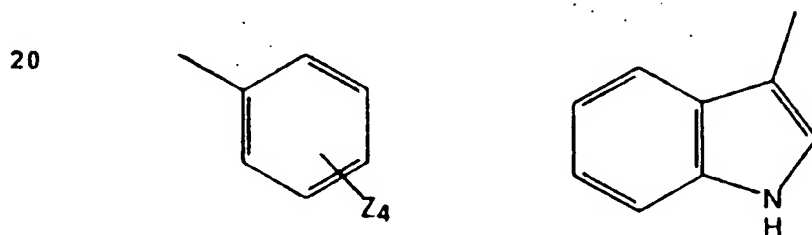


wherein

Z<sub>3</sub> is from 1 to 3 substituents each independently chosen from the group consisting of hydrogen, halogen, benzyloxy, hydroxy, CF<sub>3</sub>, C<sub>1</sub>-C<sub>4</sub> alkyl, and C<sub>1</sub>-C<sub>4</sub> alkoxy; R<sub>6</sub> is hydrogen, C<sub>1</sub>-C<sub>4</sub> alkyl, or -CHO;

15

R<sub>1</sub> is hydrogen, C<sub>1</sub>-C<sub>4</sub> alkyl, -(CH<sub>2</sub>)<sub>q</sub>Ar<sub>4</sub>, or -CH<sub>2</sub>C(O)Ar<sub>4</sub> wherein q is an integer from 1 to 4 and Ar<sub>4</sub> is a radical of the formula



wherein

Z<sub>4</sub> is from 1 to 3 substituents each independently chosen from the group consisting of hydrogen, halogen, benzyloxy, hydroxy, CF<sub>3</sub>, C<sub>1</sub>-C<sub>4</sub> alkyl, and C<sub>1</sub>-C<sub>4</sub> alkoxy;

30

or stereoisomers, or pharmaceutically acceptable salt thereof;

with the proviso that, when G<sub>1</sub> is -C(O)-, then G<sub>2</sub> is not  
35 -C(O)-;

-4-

and with the further proviso that, when  $G_3$  is  $-\text{CH}_2-$ , then  $G_1$  and  $G_2$  are  $-\text{CH}_2-$ .

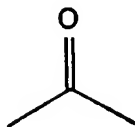
As is appreciated by one of ordinary skill in the art the compounds of the formula (1) exist as stereoisomers. The Cahn-Ingold-Prelog designation of (R)- and (S)- for the stereochemistry of compounds represented by formula (1) depends on the nature of the substituents present. Any reference in this application to one of the compounds of the formula (1) is meant to encompass either specific stereoisomers or a mixture of stereoisomers. The specific stereoisomers can be prepared by stereospecific synthesis or can be separated and recovered by techniques known in the art, such as chromatography on chiral stationary phases, amide formation with a chiral acid followed by separation of the resultant diastereomeric amides and hydrolysis to the desired stereoisomer, or fractional recrystallization of addition salts formed by reagents used for that purpose, as described in "Enantiomers, Racemates, and Resolutions", J. Jacques, A. Collet, and S. H. Wilen, Wiley (1981).

As used in this application:

- a) the term "halogen" refers to a fluorine atom, chlorine atom, bromine atom, or iodine atom;
- b) the term " $\text{C}_1\text{-C}_4$  alkyl" refer to a branched or straight chained alkyl radical containing from 1 to 4 carbon atoms, such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, t-butyl, etc;
- c) the term " $\text{C}_1\text{-C}_4$  alkoxy" refer to a straight or branched alkoxy group containing from 1 to 4 carbon atoms, such as methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, t-butoxy, etc;

-5-

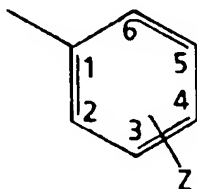
d) the designation -C(O)- or C(O) refers to a carbonyl group of the formula:



e) the designation "~~~~" refers to a bond for which the stereochemistry is not designated.

10 f) as used in the preparations and examples: the term "mg" refers to milligrams; the term "g" refers to grams; the term "kg" refers to kilograms; the term "mmol" refers to millimoles; the term "mL" refers to milliliters; the term "°C" refers to degrees Celsius the term "R<sub>f</sub>" refers to  
15 retention factor; the term "mp" refers to melting point; the term "dec" refers to decomposition; the term "THF" refers to tetrahydrofuran; the term "DMF" refers to dimethylformamide; the term "[α]<sub>D</sub><sup>20</sup>" refer to specific rotation of the D line of sodium at 20° C obtained in a 1 decimeter cell; the term  
20 "c" refers to concentration in g/mL; the term "DMSO" refers to dimethyl sulfoxide; the term "M" refers to molar; the term "HPLC" refers to high performance liquid chromatography; the term "HRMS" refers to high resolution  
25 mass spectrum;

g) by the designation

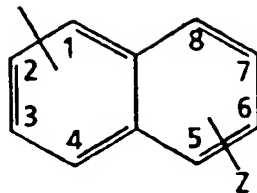


35 it is understood that the radical is attached at the 1-position and the substituent or substituents represented by Z can be attached in any of the 2, 3, 4, 5, or 6 positions;

-6-

h) by th designation

5



it is understood that the radical can be attached at the  
10 either the 1-position or the 2-position, it is further  
understood that when the radical is attached at the 1-  
position the substituent or substituents represented by 2  
can be attached in any of the 2, 3, 4, 5, 6, 7, or 8  
positions and that when the radical is attached at the 2-  
15 position the substituent or substituents represented by 2  
can be attached in any of the 1, 3, 4, 5, 6, 7, or 8  
positions;

i) the term "pharmaceutically acceptable salts thereof"  
20 refers to either an acid addition salt or a basic addition  
salt.

The expression "pharmaceutically acceptable acid addi-  
tion salts" is intended to apply to any non-toxic organic or  
25 inorganic acid addition salt of the base compounds  
represented by formula (1) or any of its intermediates.  
Illustrative inorganic acids which form suitable salts  
include hydrochloric, hydrobromic, sulphuric, and phosphoric  
acid and acid metal salts such as sodium monohydrogen  
30 orthophosphate, and potassium hydrogen sulfate.  
Illustrative organic acids which form suitable salts include  
the mono-, di-, and tricarboxylic acids. Illustrative of  
such acids are for example, acetic, glycolic, lactic,  
pyruvic, malonic, succinic, glutaric, fumaric, malic,  
35 tartaric, citric, ascorbic, maleic, hydroxymaleic, benzoic,  
hydroxy-benzoic, phenylacetic, cinnamic, salicylic, 2-  
phenoxy-benzoic, p-toluenesulfonic acid, and sulfonic acids

-7-

such as methane sulfonic acid and 2-hydroxyethane sulfonic acid. Such salts can exist in either a hydrated or substantially anhydrous form. In general, the acid addition salts of these compounds are soluble in water and various hydrophilic organic solvents, and which in comparison to their free base forms, generally demonstrate higher melting points.

The expression "pharmaceutically acceptable basic addition salts" is intended to apply to any non-toxic organic or inorganic basic addition salts of the compounds represented by formula (1) or any of its intermediates. Illustrative bases which form suitable salts include alkali metal or alkaline-earth metal hydroxides such as sodium, potassium, calcium, magnesium, or barium hydroxides; ammonia, and aliphatic, alicyclic, or aromatic organic amines such as methylamine, dimethylamine, trimethylamine, and picoline. Either the mono- or di-basic salts can be formed with those compounds.

20

As with any group of structurally related compounds which possesses a particular generic utility, certain groups and configurations are preferred for the compounds of formula (1) in their end-use application.

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Preferred embodiments of formula (1) are given below:

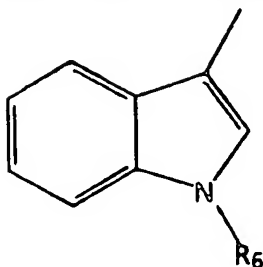
- 1) Compounds in which  $G_3$  is  $-C(O)-$  are preferred;
- 2) Compounds in which  $G_1$  is  $-C(O)-$  and  $G_2$   $-CH_2-$  are preferred, and compounds in which  $G_1$  is  $-CH_2-$  and  $G_2$  is  $-C(O)-$  are more preferred;
- 3) Compounds in which  $R_1$  is hydrogen are preferred.

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-8-

4) Compounds in which Ar<sub>3</sub> is the radical

5



10 are preferred.

It is understood that further preferred embodiments of formula (1) can be selected by requiring one or more of the preferred embodiments 1 through 4 of formula (1) or by  
15 reference to examples given herein.

Illustrative of compounds encompassed by the present invention include the following. This list is meant to be representative only and is not intended to limit the scope  
20 of the invention in any way:

(S)-2-[(S)-3-(1H-Indol-3-ylmethyl)-2-oxo-piperazin-1-yl]-1-[N-methyl-N-benzyl-3-(phenyl)-propionamide];

25 (S)-2-[(S)-3-(1-Methyl-indol-3-ylmethyl)-2-oxo-piperazin-1-yl]-1-[N-methyl-N-benzyl-3-(phenyl)-propionamide];

(S)-2-[(R)-3-(1H-Indol-3-ylmethyl)-2-oxo-piperazin-1-yl]-1-[N-methyl-N-benzyl-3-(phenyl)-propionamide];

30

(S)-2-[(S)-3-phenylmethyl-2-oxo-piperazin-1-yl]-1-[N-methyl-N-benzyl-3-(phenyl)-propionamide];

(S)-2-[(S)-3-phenyl-2-oxo-piperazin-1-yl]-1-[N-methyl-N-benzyl-3-(phenyl)-propionamide];  
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-9-

- (S)-2-[(S)-3-(1H-Indol-3-ylmethyl)-2-oxo-piperazin-1-yl]-1-[N-methyl-N-benzyl-3-(naphth-2-yl)-propionamide];
- (S)-2-[(S)-3-(1H-Indol-3-ylmethyl)-2-oxo-piperazin-1-yl]-1-  
5 [N-methyl-N-(2-methoxybenzyl)-3-(naphth-2-yl)-propionamide];
- (S)-2-[(S)-3-(1H-Indol-3-ylmethyl)-2-oxo-piperazin-1-yl]-1-[N-methyl-N-(3,4-dichlorobenzyl)-3-(naphth-2-yl)-  
10 propionamide];
- (S)-2-[(S)-3-(1H-Indol-3-ylmethyl)-2-oxo-piperazin-1-yl]-1-[N-methyl-N-(2-methoxybenzyl)-3-(phenyl)-propionamide];
- 15 (S)-2-[3-(1H-Indol-3-ylmethyl)-2-oxo-piperazin-1-yl]-2-[[S)-N-methyl-N-(3-phenyl-propyl)]-benzamide];
- (S)-2-[3-(1H-Indol-3-ylmethyl)-2-oxo-piperazin-1-yl]-[(S)-N-methyl-N-benzyl-3-(phenyl)-propylamine];  
20
- (R)-2-[(S)-3-(1H-Indol-3-ylmethyl)-piperazin-1-yl]-1-[N-methyl-N-benzyl-3-(phenyl)-propionamide];
- (R)-2-[(S)-3-(1H-Indol-3-ylmethyl)-2-oxo-piperazin-1-yl]-1-  
25 [N-methyl-N-benzyl-3-(phenyl)-propionamide];
- (R)-2-[(S)-3-(1-Methyl-indol-3-ylmethyl)-2-oxo-piperazin-1-yl]-1-[N-methyl-N-benzyl-3-(phenyl)-propionamide];
- 30 (R)-2-[(S)-3-(1H-Indol-3-ylmethyl)-2-oxo-piperazin-1-yl]-1-[N-methyl-N-benzyl-3-(phenyl)-propionamide];
- (R)-2-[(S)-3-phenylmethyl-2-oxo-piperazin-1-yl]-1-[N-methyl-N-benzyl-3-(phenyl)-propionamide];  
35
- (R)-2-[(S)-3-phenyl-2-oxo-piperazin-1-yl]-1-[N-methyl-N-benzyl-3-(phenyl)-propionamide];

-10-

- (R)-2-[(S)-3-(1H-Indol-3-ylmethyl)-2-oxo-piperazin-1-yl]-1-[N-methyl-N-benzyl-3-(naphth-2-yl)-propionamide];
- 5 (R)-2-[(S)-3-(1H-Indol-3-ylmethyl)-2-oxo-piperazin-1-yl]-1-[N-methyl-N-(2-methoxybenzyl)-3-(naphth-2-yl)-propionamide];
- (R)-2-[(S)-3-(1H-Indol-3-ylmethyl)-2-oxo-piperazin-1-yl]-1-  
10 [N-methyl-N-(3,4-dichlorobenzyl)-3-(naphth-2-yl)-propionamide];
- (R)-2-[(S)-3-phenyl-2-oxo-piperazin-1-yl]-1-[N-methyl-N-(2-methoxybenzyl)-3-(phenyl)-propionamide];
- 15 (R)-2-[3-(1H-Indol-3-ylmethyl)-2-oxo-piperazin-1-yl]-2-[[ (S)-N-methyl-N-(3-phenyl-propyl)]-benzamide];
- (R)-2-[3-(1H-Indol-3-ylmethyl)-2-oxo-piperazin-1-yl]-[(S)-  
20 N-methyl-N-benzyl-3-(phenyl)-propylamine];
- (R)-2-[(S)-3-(1H-Indol-3-ylmethyl)-piperazin-1-yl]-1-[N-methyl-N-benzyl-3-(phenyl)-propionamide];
- 25 (S)-2-[(R)-3-(1H-Indol-3-ylmethyl)-2-oxo-piperazin-1-yl]-1-[N-methyl-N-benzyl-3-(phenyl)-propionamide];
- (S)-2-[(R)-3-(1-Methyl-indol-3-ylmethyl)-2-oxo-piperazin-1-yl]-1-[N-methyl-N-benzyl-3-(phenyl)-propionamide];
- 30 (S)-2-[(R)-3-(1H-Indol-3-ylmethyl)-2-oxo-piperazin-1-yl]-1-[N-methyl-N-benzyl-3-(phenyl)-propionamide];
- (S)-2-[(R)-3-phenylmethyl-2-oxo-piperazin-1-yl]-1-[N-methyl-N-benzyl-3-(phenyl)-propionamide];
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-11-

(S)-2-[(R)-3-phenyl-2-oxo-piperazin-1-yl]-1-[N-methyl-N-benzyl-3-(phenyl)-propionamide];

5 (S)-2-[(R)-3-(1H-Indol-3-ylmethyl)-2-oxo-piperazin-1-yl]-1-[N-methyl-N-benzyl-3-(naphth-2-yl)-propionamide];

(S)-2-[(R)-3-(1H-Indol-3-ylmethyl)-2-oxo-piperazin-1-yl]-1-[N-methyl-N-(2-methoxybenzyl)-3-(naphth-2-yl)-propionamide];

10 (S)-2-[(R)-3-(1H-Indol-3-ylmethyl)-2-oxo-piperazin-1-yl]-1-[N-methyl-N-(3,4-dichlorobenzyl)-3-(naphth-2-yl)-propionamide];

15 (S)-2-[(R)-3-phenyl-2-oxo-piperazin-1-yl]-1-[N-methyl-N-(2-methoxybenzyl)-3-(phenyl)-propionamide];

(S)-2-[3-(1H-Indol-3-ylmethyl)-2-oxo-piperazin-1-yl]-2-[[ (R)-N-methyl-N-(3-phenyl-propyl)]-benzamide];

20 (S)-2-[3-(1H-Indol-3-ylmethyl)-2-oxo-piperazin-1-yl]-[(R)-N-methyl-N-benzyl-3-(phenyl)-propylamine];

(S)-2-[(R)-3-(1H-Indol-3-ylmethyl)-piperazin-1-yl]-1-[N-methyl-N-benzyl-3-(phenyl)-propionamide];

25 (R)-2-[(R)-3-(1H-Indol-3-ylmethyl)-2-oxo-piperazin-1-yl]-1-[N-methyl-N-benzyl-3-(phenyl)-propionamide];

30 (R)-2-[(R)-3-(1-Methyl-indol-3-ylmethyl)-2-oxo-piperazin-1-yl]-1-[N-methyl-N-benzyl-3-(phenyl)-propionamide];

(R)-2-[(R)-3-(1H-Indol-3-ylmethyl)-2-oxo-piperazin-1-yl]-1-[N-methyl-N-benzyl-3-(phenyl)-propionamide];

35 (R)-2-[(R)-3-phenylmethyl-2-oxo-piperazin-1-yl]-1-[N-methyl-N-benzyl-3-(phenyl)-propionamide];

-12-

(R)-2-[(R)-3-phenyl-2-oxo-piperazin-1-yl]-1-[N-methyl-N-benzyl-3-(phenyl)-propionamide];

5 (R)-2-[(R)-3-(1H-Indol-3-ylmethyl)-2-oxo-piperazin-1-yl]-1-[N-methyl-N-benzyl-3-(naphth-2-yl)-propionamide];

(R)-2-[(R)-3-(1H-Indol-3-ylmethyl)-2-oxo-piperazin-1-yl]-1-[N-methyl-N-(2-methoxybenzyl)-3-(naphth-2-yl)-  
10 propionamide];

(R)-2-[(R)-3-(1H-Indol-3-ylmethyl)-2-oxo-piperazin-1-yl]-1-[N-methyl-N-(3,4-dichlorobenzyl)-3-(naphth-2-yl)-  
propionamide];

15 (R)-2-[(R)-3-phenyl-2-oxo-piperazin-1-yl]-1-[N-methyl-N-(2-methoxybenzyl)-3-(phenyl)-propionamide];

(R)-2-[3-(1H-Indol-3-ylmethyl)-2-oxo-piperazin-1-yl]-2-  
20 [(R)-N-methyl-N-(3-phenyl-propyl)]-benzamide];

(R)-2-[3-(1H-Indol-3-ylmethyl)-2-oxo-piperazin-1-yl]-[(R)-N-methyl-N-benzyl-3-(phenyl)-propylamine];

25 (R)-2-[(R)-3-(1H-Indol-3-ylmethyl)-piperazin-1-yl]-1-[N-methyl-N-benzyl-3-(phenyl)-propionamide].

The compounds of formula (1) may be synthesized by use of the following synthetic procedures to produce  
30 intermediates or final compounds of the invention:

- Scheme A.1 relates to the synthesis of compounds of formula (1) in which G<sub>3</sub> is -C(O)-.

35 Scheme A.2 relates to the synthesis of compounds of formula (1) in which G<sub>3</sub> is -CH<sub>2</sub>-.

-13-

Scheme B relates to the synthesis of the aldehyde of structure (3) in which  $G_1$  is  $-CH_2-$  and  $G_2$  is  $-C(O)-$  used as a starting material in Scheme A.1.

- 5     •     Scheme C relates to the synthesis of the aldehyde of structure (3) in which  $G_1$  is  $-C(O)-$  and  $G_2$  is  $-CH_2-$  used as a starting material in Scheme A.1.
- 10     •     Scheme D relates to the synthesis of the aldehyde of structure (3) in which  $G_1$  is  $-CH_2-$  and  $G_2$  is  $-CH_2-$  used as a starting material in Scheme A.1.

A general synthetic procedure for preparing these compounds of formula (1) in which  $G_3$  is  $-C(O)-$  is set forth  
15 in Scheme A.1. The reagents and starting materials are readily available to one of ordinary skill in the art. In Scheme A.1, all substituents, unless otherwise indicated, are as previously defined.

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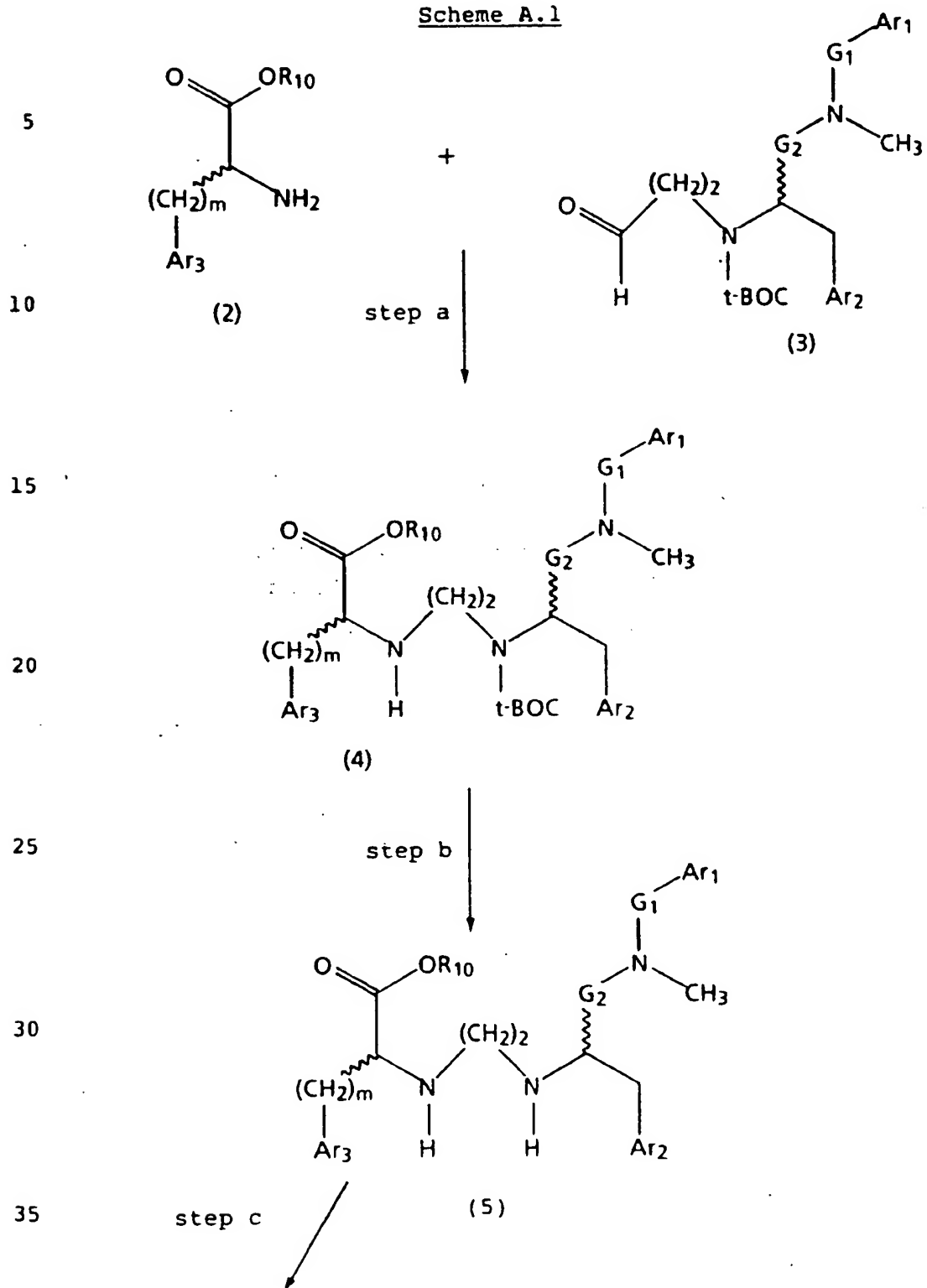
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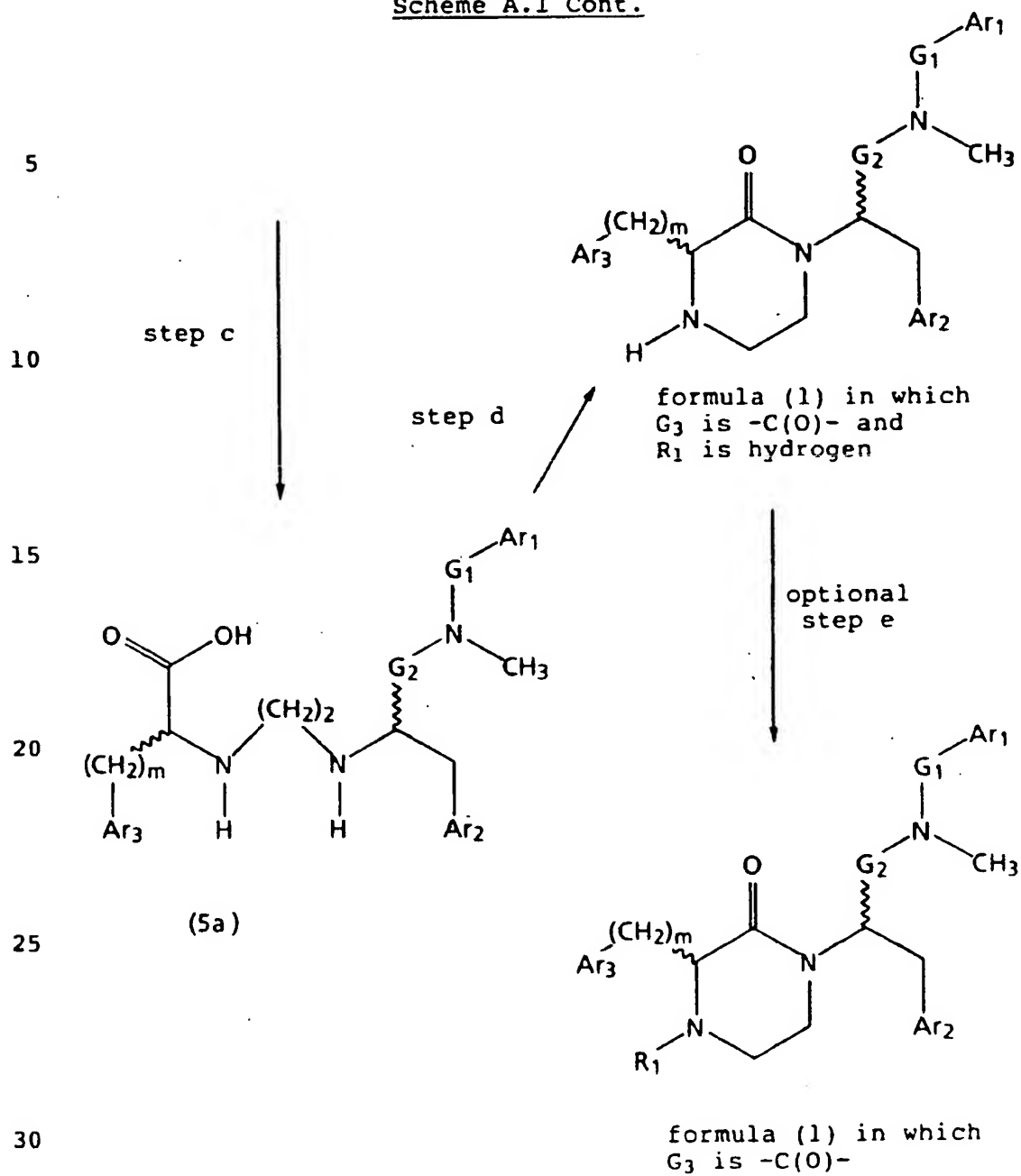
-14-

Scheme A.1



-15-

## Scheme A.1 Cont.



In Scheme A.1, step a, an appropriate aldehyde of structure (3) is contacted with an appropriate amine of structure (2) or a salt thereof in a reductive amination to give a compound of structure (4).

-16-

An appropriate aldehyde of structure (3) is one in which stereochemistry,  $G_1$ ,  $G_2$ ,  $Ar_1$ , and  $Ar_2$  are as desired in the product of formula (1) or can also be one in which the stereochemistry,  $Ar_1$ , and  $Ar_2$  give rise after  
5 resolution, deprotection, or modification to stereochemistry,  $Ar_1$ , and  $Ar_2$  as desired in the final product of formula (1).

An appropriate amine of structure (2) is one in which  
10  $R_{10}$  is a  $C_1$ - $C_4$  alkyl, with compounds of structure (2) in which  $R_{10}$  is methyl being preferred, stereochemistry,  $m$ , and  $Ar_3$  are as desired in the final product of formula (1) or can also be one in which the stereochemistry and  $Ar_3$  give rise after resolution, deprotection, or modification to  
15 stereochemistry and  $Ar_3$  as desired in the final product of formula (1).

For example, an appropriate aldehyde of structure (3) is contacted with an appropriate amine of structure (2) or  
20 a salt of an appropriate amine of structure (2) in a reductive amination. The reaction is carried out using a molar excess of a suitable reducing agent such as sodium borohydride or sodium cyanoborohydride with sodium cyanoborohydride being preferred. The reaction is carried  
25 out in a suitable solvent, such as methanol. The reaction is carried out at temperatures of from  $0^\circ\text{C}$  to  $50^\circ\text{C}$ . The reaction generally requires 1 to 72 hours. The product can be isolated and purified by techniques well known in the art, such as extraction, evaporation, chromatography, and  
30 recrystallization.

In Scheme A.1, step b, the compound of structure (4) is deprotected to give a diamino ester of structure (5).

35 For example, a compound of structure (4) is reacted with a protic acid, such as hydrochloric acid or trifluoroacetic acid. The reaction is carried out in a

-17-

solvent, such as ethyl acetate, dioxane, methanol, or ethanol. The reaction generally requires from 1 to 48 hours and is carried out at ambient temperature. The product can be isolated and purified by techniques well known in the art, such as extraction, evaporation, chromatography, and recrystallization.

In Scheme A.1, step c, a ester diamino ester of structure (5) in which  $R_{10}$  is  $C_1-C_4$  alkyl is hydrolyzed to give an acid diamino acid of structure (5a). The hydrolysis of esters, such as those described in Protecting Groups in Organic Synthesis by T. Greene is well known and appreciated in the art. As is appreciated by one of ordinary skill in the art, steps b and c can be carried out in any order.

For example, a diamino ester of structure (5) in which  $R_{10}$  is  $C_1-C_4$  alkyl is reacted with a suitable hydrolyzing agent, such as sodium hydroxide, potassium hydroxide, lithium hydroxide, or sodium carbonate. The reaction is carried out in a suitable solvent, such as water or water/methanol mixtures, water/ethanol mixtures, water/tetrahydrofuran mixtures. The reactions are carried out at temperatures of from  $0^\circ\text{C}$  to the refluxing temperature of the solvent and generally require from 30 minutes to 48 hours. The product can be isolated and purified by techniques well known in the art, such as acidification, extraction, evaporation, chromatography, and recrystallization.

30

In Scheme A.1, step d, a diamino acid of structure (5a) or a salt thereof undergoes a cyclization reaction to give a compound of the formula (1) in which  $G_3$  is  $-\text{C}(\text{O})-$  and  $R_1$  is hydrogen. This cyclization reaction may be carried out in the presence of coupling reagents, such as 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline or 1,3-dicyclohexylcarbodiimide or may proceed through an

-18-

activated intermediate, such as (O)-hydroxybenzotriazole, which may be prepared but is not necessarily isolated before the cyclization.

5 For example, a diamino acid of structure (5a) or a salt thereof is contacted with 1-hydroxybenzotriazole hydrate in the presence of a slight molar excess of a coupling agent, such as dicyclohexylcarbodiimide or 1-(3-  
10 dimethylaminopropyl)-3-ethylcarbodiimide. The reaction is carried out in the presence of a suitable base, such as diisopropylethyl amine. The reaction is carried out in a suitable solvent, such as dichloromethane or chloroform. The reaction is carried out at temperatures of from -50°C to the refluxing temperature of the solvent. The reaction  
15 generally requires from 1 hour to 48 hours. The product can be isolated and purified by techniques well known in the art, such as extraction, evaporation, chromatography, and recrystallization.

20 In Scheme A.1, optional step e, a protected compound of formula (1) may be deprotected or modified to give a compound of formula (1).

A deprotection reaction encompasses the removal of a  
25 hydroxy protecting group. The selection, use, and removal of protecting groups utilizing suitable protecting groups such as those described in Protecting Groups in Organic Synthesis by T. Greene is well known and appreciated in the art.

30

A modification reaction encompasses the alkylation of an amine, an addition reaction to an indole nitrogen, or the formation of an amidate. A compound of formula (1) in which G<sub>3</sub> is -C(O)- and R<sub>1</sub> is hydrogen is alkylated with an  
35 appropriate alkylating agent to give a compound of formula (1) in which R<sub>1</sub> is C<sub>1</sub>-C<sub>4</sub> alkyl, -(CH<sub>2</sub>)<sub>q</sub>Ar<sub>4</sub>, or -CH<sub>2</sub>C(O)Ar<sub>4</sub>. An appropriate alkylating agent is one which transfers a C<sub>1</sub>-



-19-

C<sub>4</sub> alkyl, -(CH<sub>2</sub>)<sub>q</sub>Ar<sub>4</sub>, or -CH<sub>2</sub>C(O)Ar<sub>4</sub>, such as iodomethane, bromomethane, bromoethane, bromopropane, bromobutane, benzylbromide, benzylchloride, phenethylbromide, 3-chloro-1-phenyl-propane, 4-chloro-1-phenyl-butane, α-chloroacetophenone, α-bromoacetophenone, 3-[(chloro)acetyl]-indole, etc. Modification reactions involving the alkylation of an indole nitrogen carried out on compounds of formula (1) in which R<sub>1</sub> is hydrogen may require the use of a protecting group. When this is the case a t-BOC protecting group may be used. The use and removal of the t-BOC protecting group as described in Protecting Groups in Organic Synthesis by T. Greene is well known and appreciated in the art.

For example, a modification may involve a compound of formula (1) in which R<sub>1</sub> is hydrogen is contacted with a slight molar amount of an appropriate alkylating agent. The reaction is carried out in the presence of a slight molar excess of a suitable base, such as sodium bicarbonate, potassium bicarbonate, diisopropylethyl amine or triethyl amine. The reaction is carried out in a suitable solvent, such as acetonitrile, dimethylformamide, ethanol, or dimethyl sulfoxide. The reaction may be carried out in the presence of a suitable catalyst, such as potassium iodide, sodium iodide, tetrabutylammonium iodide, trimethylbenzylammonium iodide, tetraethylammonium iodide, tetrabutylammonium bromide, trimethylbenzylammonium bromide, tetraethylammonium bromide, tetrabutylammonium hydrogen sulfate, trimethylbenzylammonium hydrogen sulfate, tetraethylammonium hydrogen sulfate, etc. The reaction is carried out at temperatures of from 50°C to the reflux temperature of the solvent. The reaction generally requires from 1 to 48 hours. The product can be isolated and purified by techniques well known in the art, such as extraction, evaporation, chromatography, and recrystallization.

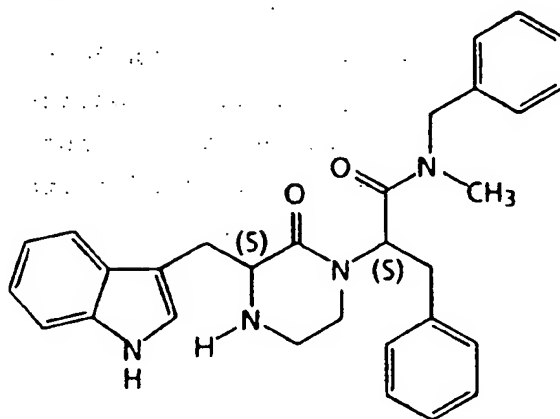
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As is well known and appreciated in the art, a number of protection, deprotection, and modification steps encompassed by Scheme A.1 optional step e may be required and may be carried out in any order which allows for the proper incorporation of groups as desired in the final product of formula (1).

The following examples present typical syntheses as described in Scheme A.1. These examples are understood to be illustrative only and are not intended to limit the scope of the invention in any way.

EXAMPLE 1

(S)-2-[(S)-3-(1H-Indol-3-ylmethyl)-2-oxo-piperazin-1-yl]-1-[N-methyl-N-benzyl-3-(phenyl)-propionamide]



Scheme A.1, step a: (S)-N-Benzyl-N-methyl-2-[[[(S)-2-[(1H-indol-3-yl)-1-carboxymethyl]-ethylamino]-N'-(t-butoxycarbonyl)-ethylamino]-3-phenyl-propionamide]

Combine (S)-N-benzyl-N-methyl-2-[N'-(t-butoxycarbonyl)-2-oxo-ethylamino]-3-phenyl-propionamide (4.87 g, 11.87 mmol) and (S)-2-(1H-indol-3-yl)-1-carboxymethyl-ethylamine hydrochloride salt ((S)-tryptophan methyl ester hydrochloride salt) (3.02 g, 11.86 mmol) in methanol (120 mL). Add sodium cyanoborohydride in solution (9.5 mL, 1M in THF, 9.5 mmol) and stir under an inert atmosphere for 48 hours. Concentrate *in vacuo* to obtain a residue. Dilute the

-21-

residue with ethyl acetate and extract with water. Separate the layers, dry the organic layer over  $\text{MgSO}_4$ , filter, and evaporate *in vacuo*. Chromatograph on silica gel eluting with 3% methanol/dichloromethane to give the title compound: TLC  $R_f=0.57$  (silica gel, 10% methanol/dichloromethane).

10 Scheme A.1, step b: (S)-N-Benzyl-N-methyl-2-[[[(S)-2-(1H-indol-3-yl)-1-carboxymethyl-ethylamino]-ethylamino]-3-phenyl-propionamide

Combine (S)-N-benzyl-N-methyl-2-[[[(S)-2-(1H-indol-3-yl)-1-carboxymethyl-ethylamino]-N'-(t-butoxycarbonyl)-ethylamino]-3-phenyl-propionamide (0.28 g, 0.58 mmol) and 4M dioxane (10 mL) and stir for 1 hour. Evaporate *in vacuo*. Purify by chromatography on silica gel eluting sequentially with dichloromethane and then 3% methanol/ dichloromethane to give the title compound: TLC  $R_f=0.51$  (silica gel, 10% methanol/dichloromethane). HRMS calculated for  $\text{C}_{29}\text{H}_{36}\text{N}_3\text{O}_3$  474.2757. Found 474.2755.

20

Scheme A.1, step c: (S)-N-Benzyl-N-methyl-2-[[[(S)-2-(1H-indol-3-yl)-1-carboxy-ethylamino]-ethylamino]-3-phenyl-propionamide

Combine (S)-N-benzyl-N-methyl-2-[[[(S)-2-(1H-indol-3-yl)-1-carboxymethyl-ethylamino]ethylamino]-3-phenyl-propionamide (0.48 g, 0.93 mmol) and 1M sodium hydroxide (10 mL, 10 mmol) in ethanol (20 mL) and stir under an inert atmosphere for 18 hours. Dilute with water and extract with ethyl acetate. Acidify the aqueous layer with 1N hydrochloric acid and extract with ethyl acetate. Dry the organic layer over  $\text{MgSO}_4$ , filter and evaporate *in vacuo* to give the title compound as a solid: TLC  $R_f=0.43$  (silica gel, 85% chloroform, 10% methanol, 5% acetic acid). HRMS calculated for  $\text{C}_{30}\text{H}_{35}\text{N}_4\text{O}_3$  499.2709. Found 499.2696.

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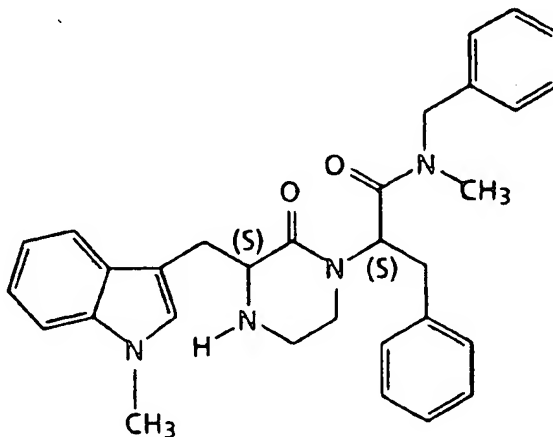
-22-

Scheme A.1, step d: (S)-2-[(S)-3-(1H-Indol-3-ylmethyl)-2-oxo-piperazin-1-yl]-1-[N-methyl-N-benzyl-3-(phenyl)-propionamide]

Combine (S)-N-benzyl-N-methyl-2-[[[(S)-2-(1H-indol-3-yl)-1-carboxy-ethylamino]-ethylamino]-3-phenyl-propionamide (0.10 g, 0.20 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.043 g, 0.22 mmol), 1-hydroxybenzotriazole hydrate (0.033 g, 0.22 mmol), diisopropylethylamine (0.053 mL, 0.22 mmol) and dimethylformamide (2 mL). Stir under an inert atmosphere for 18 hours. Dilute with ethyl acetate and extract with water. Dry the organic layer over MgSO<sub>4</sub>, filter, and evaporate *in vacuo*. Chromatograph eluting sequentially with 50% ethyl acetate/hexane, ethyl acetate, and 5% methanol/dichloromethane to give the title compound: TLC R<sub>f</sub>=0.51 (silica gel, 10% methanol/dichloromethane). HRMS calculated for C<sub>30</sub>H<sub>33</sub>N<sub>4</sub>O<sub>2</sub> 481.2604. Found 481.2582

#### EXAMPLE 2

(S)-2-[(S)-3-(1-Methyl-indol-3-ylmethyl)-2-oxo-piperazin-1-yl]-1-[N-methyl-N-benzyl-3-(phenyl)-propionamide]



Scheme A.1, step a: (S)-N-Benzyl-N-methyl-2-[[[(S)-2-[(1-methyl-indol-3-yl)-1-carboxymethyl]-ethylamino]-N'-(t-butoxycarbonyl)-ethylamino]-3-phenyl-propionamide]

Prepare by the method of Example 1, Scheme A.1, step a, using (S)-2-(1-methyl-indol-3-yl)-1-carboxymethyl-

-23-

ethylamine hydrochloride salt (Lin-Hua Zhang and James M. Cook Heterocycles 27, 2795-2802 (1988)) (1.0 mmol) and (S)-N-benzyl-N-methyl-2-[N'-(t-butoxycarbonyl)-2-oxo-ethylamino]-3-phenyl-propionamide (1.0 mmol) to give the  
5 title compound.

Scheme A.1, step b: (S)-N-Benzyl-N-methyl-2-[[[(S)-2-[(1-methyl-indol-3-yl)-1-carboxymethyl]-ethylamino]-ethylamino]-3-phenyl-propionamide

10 Prepare by the method of Example 1, Scheme A.1, step b, using (S)-N-Benzyl-N-methyl-2-[[[(S)-2-[(1-methyl-indol-3-yl)-1-carboxymethyl]-ethylamino]-N'-(t-butoxycarbonyl)-ethylamino]-3-phenyl-propionamide to give the title compound.

15

Scheme A.1, step c: (S)-N-Benzyl-N-methyl-2-[[[(S)-2-[(1-methyl-indol-3-yl)-1-carboxy]-ethylamino]-ethylamino]-3-phenyl-propionamide

20 Prepare by the method of Example 1, Scheme A.1, step c, using (S)-N-Benzyl-N-methyl-2-[[[(S)-2-[(1-methyl-indol-3-yl)-1-carboxymethyl]-ethylamino]-ethylamino]-3-phenyl-propionamide to give the title compound.

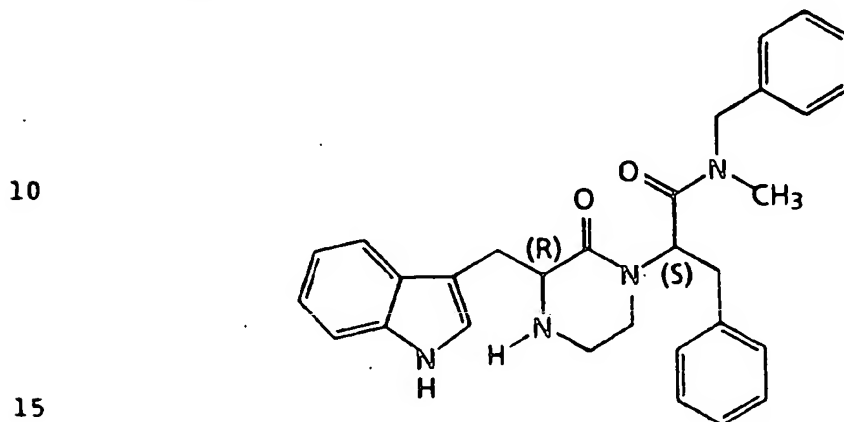
25 Scheme A.1, step d: (S)-2-[3-(1-Methyl-indol-3-ylmethyl)-2-oxo-piperazin-1-yl]-1-[N-methyl-N-benzyl-3-(phenyl)-propionamide]

30 Prepare by the method of Example 1, Scheme A.1, step d, using (S)-N-Benzyl-N-methyl-2-[[[(S)-2-[(1-methyl-indol-3-yl)-1-carboxy]-ethylamino]-ethylamino]-3-phenyl-propionamide to give the title compound.

35

EXAMPLE 3

(S)-2-[(R)-3-(1H-Indol-3-ylmethyl)-2-oxo-piperazin-1-yl]-1-  
[N-methyl-N-benzyl-3-(phenyl)-propionamide]



Scheme A.1, step a: (S)-N-Benzyl-N-methyl-2-[[[(R)-2-[(1H-  
indol-3-yl)-1-carboxymethyl]-ethylamino]-N'-(t-  
butoxycarbonyl)-ethylamino]-3-phenyl-propionamide

Prepare by the method of Example 1, Scheme A.1, step a, using (R)-2-(1H-indol-3-yl)-1-carboxymethyl-ethylamine hydrochloride salt ((R)-tryptophan methyl ester hydrochloride salt) (0.25 g, 1.0 mmol) and (S)-N-benzyl-N-methyl-2-[N'-(t-butoxycarbonyl)-2-oxo-ethylamino]-3-phenyl-propionamide (0.41 g, 1.0 mmol) to give the title compound: TLC  $R_f$ =0.54 (silica gel, 10% methanol/dichloromethane).

Scheme A.1, step b: (S)-N-Benzyl-N-methyl-2-[[[(R)-2-(1H-  
indol-3-yl)-1-carboxymethyl-ethylamino]-ethylamino]-3-  
phenyl-propionamide

Prepare by the method of Example 1, Scheme A.1, step b, using (S)-N-benzyl-N-methyl-2-[[[(R)-2-(1H-indol-3-yl)-1-carboxymethyl-ethylamino]-N'-(t-butoxycarbonyl)-ethylamino]-3-phenyl-propionamide (0.31 g, 0.5 mmol) to give the title compound: TLC  $R_f$ =0.50 (silica gel, 10%

-25-

methanol/dichloromethane). HRMS calculated for  $C_{31}H_{37}N_4O_3$  513.2865. Found 513.2839.

5 Scheme A.1, step c: (S)-N-Benzyl-N-methyl-2-[(R)-2-(1H-indol-3-yl)-1-carboxy-ethylamino]-ethylamino]-3-phenyl-propionamide

10 Prepare by the method of Example 1, Scheme A.1, step c, using (S)-N-benzyl-N-methyl-2-[(R)-2-(1H-indol-3-yl)-1-carboxymethyl-ethylamino]-ethylamino]-3-phenyl-propionamide to give the title compound.

Scheme A.1, step d: (S)-2-[(R)-3-(1H-Indol-3-ylmethyl)-2-oxo-piperazin-1-yl]-1-[N-methyl-N-benzyl-3-(phenyl)-propionamide]

15 Prepare by the method of Example 1, Scheme A.1, step d, using (S)-N-benzyl-N-methyl-2-[(R)-2-(1H-indol-3-yl)-1-carboxy-ethylamino]-ethylamino]-3-phenyl-propionamide to give the title compound.

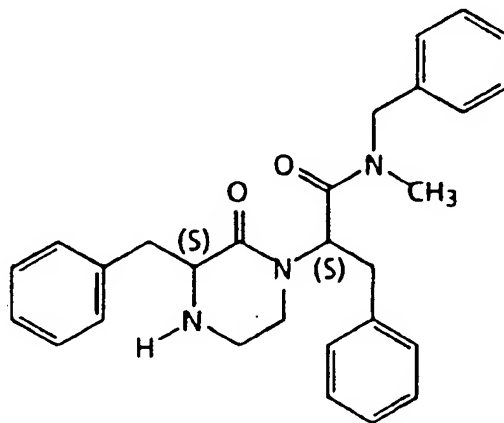
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#### EXAMPLE 4

(S)-2-[(S)-3-phenylmethyl-2-oxo-piperazin-1-yl]-1-[N-methyl-N-benzyl-3-(phenyl)-propionamide]

25

30



35 Scheme A.1, step a: (S)-N-Benzyl-N-methyl-2-[(S)-2-phenyl-1-carboxymethyl]-ethylamino]-N'-(t-butoxycarbonyl)-ethylamino-3-phenyl-propionamide

-26-

Prepare by the method of Example 1 using (S)-2-amino-3-phenyl-propionic acid methyl ester hydrochloride salt ((S)-phenylalanine methyl ester hydrochloride salt) (0.26 g, 1.0 mmol) and (S)-N-benzyl-N-methyl-2-[N'-(t-butoxycarbonyl)-2-oxo-ethylamino]-3-phenyl-propionamide (0.41 g, 1.0 mmol) to give the title compound: TLC  $R_f$ =0.51 (silica gel, 10% methanol/dichloromethane).

Scheme A.1, step b: (S)-N-Benzyl-N-methyl-2-[[[(S)-2-phenyl-1-carboxymethyl]-ethylamino]-ethylamino-3-phenyl-propionamide]

Prepare by the method of Example 1, Scheme A.1, step b, using (S)-N-benzyl-N-methyl-2-[[[(S)-2-phenyl-1-carboxymethyl]-ethylamino]-N'-(t-butoxycarbonyl)-ethylamino-3-phenyl-propionamide to give the title compound: TLC  $R_f$ =0.51 (silica gel, 10% methanol/dichloromethane).

Scheme A.1, step c: (S)-N-Benzyl-N-methyl-2-[[[(S)-2-phenyl-1-carboxy]-ethylamino]-ethylamino-3-phenyl-propionamide]

Prepare by the method of Example 1, Scheme A.1, step c, using (S)-N-benzyl-N-methyl-2-[[[(S)-2-phenyl-1-carboxymethyl]-ethylamino]-ethylamino-3-phenyl-propionamide to give the title compound.

Scheme A.1, step d: (S)-2-[(S)-3-phenylmethyl-2-oxo-piperazin-1-yl]-1-[N-methyl-N-benzyl-3-(phenyl)-propionamide]

Prepare by the method of Example 1, Scheme A.1, step d, using (S)-N-benzyl-N-methyl-2-[[[(S)-2-phenyl-1-carboxy]-ethylamino]-ethylamino-3-phenyl-propionamide to give the title compound.

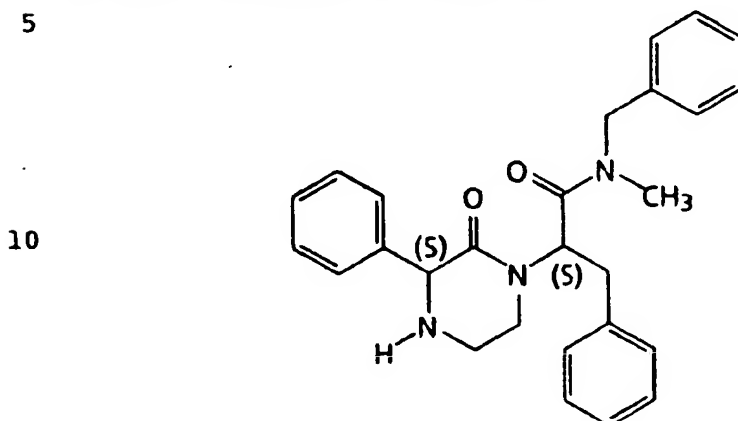
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-27-

EXAMPLE 5

(S)-2-[(S)-3-phenyl-2-oxo-piperazin-1-yl]-1-[N-methyl-N-benzyl-3-(phenyl)-propionamide]



Scheme A.1, step a: (S)-N-Benzyl-N-methyl-2-[[[(S)-1-phenyl-1-carboxymethyl-methylamino]-N'-(t-butoxycarbonyl)-ethylamino]-3-phenyl-propionamide

20 Prepare by the method of Example 1, Scheme A.1, step a, using (S)-1-amino-1-phenyl-acetic acid methyl ester hydrochloride salt ((S)-phenylglycine methyl ester hydrochloride salt) (1.0 g, 4.96 mmol) and (S)-N-benzyl-N-methyl-2-[N'-(t-butoxycarbonyl)-2-oxo-ethylamino]-3-phenyl-propionamide (2.04 g, 4.96 mmol) to give the title

25 compound: TLC  $R_f$ =0.80 (silica gel, 10% methanol/dichloromethane).

Scheme A.1, step b: (S)-N-Benzyl-N-methyl-2-[[[(S)-1-phenyl-1-carboxymethyl-methylamino]-ethylamino]-3-phenyl-propionamide

30

Prepare by the method of Example 1, Scheme A.1, step b, using (S)-N-benzyl-N-methyl-2-[[[(S)-1-phenyl-1-carboxymethylamino]-ethylamino]-3-phenyl-propionamide and purify by chromatography eluting with 5% methanol/dichloromethane to give the title compound as a colorless oil: TLC  $R_f$ =0.76

35 (silica gel, 10% methanol/dichloromethane). Elem. Anal.

-28-

calculated for  $C_{28}H_{33}N_3O_3 \cdot 0.25H_2O$ : C, 72.47; H, 7.23, N, 9.05. Found: C, 72.47; H, 7.53, N, 9.10.

Scheme A.1, step c: (S)-N-Benzyl-N-methyl-2-[[[(S)-1-phenyl-1-carboxy-methylamino]-ethylamino]-3-phenyl-propionamide

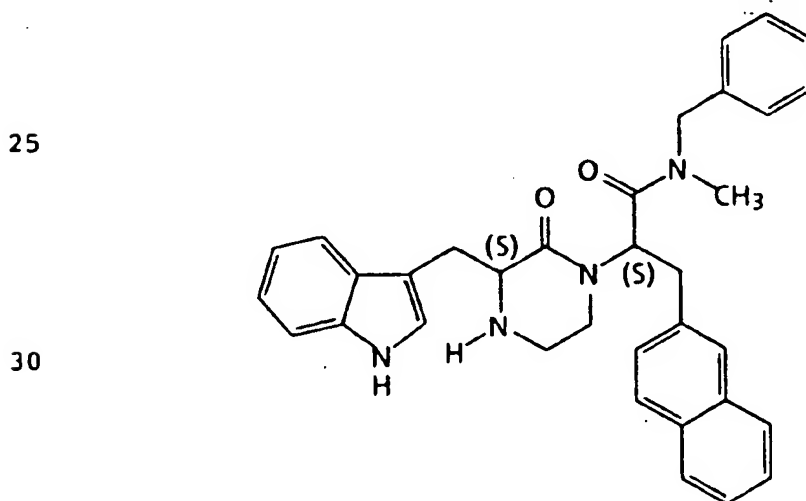
Prepare by the method of Example 1, Scheme A.1, step c, using (S)-N-benzyl-N-methyl-2-[[[(S)-1-phenyl-1-carboxymethyl-methylamino]-ethylamino]-3-phenyl-propionamide to give the title compound.

Scheme A.1, step d: (S)-2-[(S)-3-Phenyl-2-oxo-piperazin-1-yl]-1-[N-methyl-N-benzyl-3-(phenyl)-propionamide]

Prepare by the method of Example 1, Scheme A.1, step d, using (S)-N-benzyl-N-methyl-2-[[[(S)-1-phenyl-1-carboxy-methylamino]-ethylamino]-3-phenyl-propionamide to give the title compound.

#### EXAMPLE 6

(S)-2-[(S)-3-(1H-Indol-3-ylmethyl)-2-oxo-piperazin-1-yl]-1-[N-methyl-N-benzyl-3-(naphth-2-yl)-propionamide]



Scheme A.1, step a: (S)-N-Benzyl-N-methyl-2-[[[(S)-2-(1H-indol-3-yl)-1-carboxymethyl-ethylamino]-N'-(t-butoxycarbonyl)ethylamino]-3-(naphth-2-yl)-propionamide

-29-

Prepare by the method of Example 1, Scheme A.1, step a, using (S)-N-benzyl-N-methyl-2-[N'-(t-butoxycarbonyl)-2-oxo-ethylamino]-3-(2-naphthyl)-propionamide (0.46 g, 1.0 mmol) and (S)-2-(1H-indol-3-yl)-1-carboxymethyl-ethylamine hydrochloride salt ((S)-tryptophan methyl ester hydrochloride salt) (0.26 g, 1.0 mmol). Purify by chromatography eluting with 5% methanol/dichloromethane to give the title compound: TLC R<sub>f</sub>=0.34 (silica gel, 50% ethyl acetate/hexane).

10

Scheme A.1, step b: (S)-N-Benzyl-N-methyl-2-[[[(S)-2-(1H-indol-3-yl)-1-carboxymethyl-ethylamino]-ethylamino]-3-(naphth-2-yl)-propionamide

Prepare by the method of Example 1, Scheme A.1, step b, using (S)-N-benzyl-N-methyl-2-[[[(S)-2-(1H-indol-3-yl)-1-carboxymethyl-ethylamino]-N'-(t-butoxycarbonyl)ethylamino]-3-(naphth-2-yl)-propionamide to give the title compound: TLC R<sub>f</sub>=0.75 (silica gel, 85% chloroform, 10% methanol, 5% acetic acid). HRMS calculated for C<sub>35</sub>H<sub>39</sub>N<sub>4</sub>O<sub>3</sub> 563.3022. Found 563.2996.

20

Scheme A.1, step c: (S)-N-Benzyl-N-methyl-2-[[[(S)-2-(1H-indol-3-yl)-1-carboxy-ethylamino]-ethylamino]-3-(naphth-2-yl)-propionamide

Prepare by the method of Example 1, Scheme A.1, step c, using (S)-N-benzyl-N-methyl-2-[[[(S)-2-(1H-indol-3-yl)-1-carboxymethyl-ethylamino]-ethylamino]-3-(naphth-2-yl)-propionamide and purify by chromatography eluting with 5% methanol/dichloromethane to give the title compound.

30

Scheme A.1, step d: (S)-2-[(S)-3-(1H-Indol-3-ylmethyl)-2-oxo-piperazin-1-yl]-1-[N-methyl-N-benzyl-3-(naphth-2-yl)-propionamide]

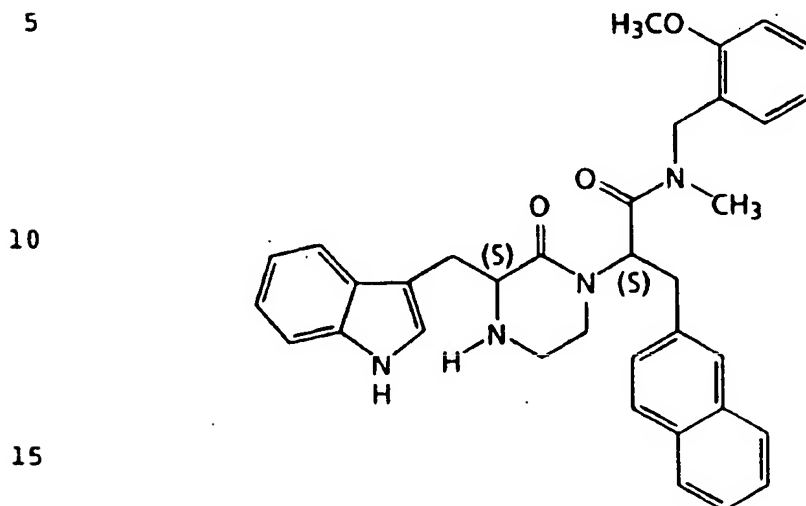
Prepare by the method of Example 1, Scheme A.1, step d, using (S)-N-benzyl-N-methyl-2-[[[(S)-2-(1H-indol-3-yl)-1-carboxy-ethylamino]-ethylamino]-3-(naphth-2-yl)-propionamide to give the title compound.

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-30-

EXAMPLE 7

(S)-2-[(S)-3-(1H-Indol-3-ylmethyl)-2-oxo-piperazin-1-yl]-1-[N-methyl-N-(2-methoxybenzyl)-3-(naphth-2-yl)-propionamide]



Scheme A.1, step a: (S)-N-(2-Methoxybenzyl)-N-methyl-2-[[[(S)-2-(1H-indol-3-yl)-1-carboxymethyl-ethylamino]-N'-(t-butoxycarbonyl)ethylamino]-3-(naphth-2-yl)-propionamide

Prepare by the method of Example 1, Scheme A.1, step a, using (S)-N-(2-methoxybenzyl)-N-methyl-2-[N'-(t-butoxycarbonyl)-2-oxo-ethylamino]-3-(naphth-2-yl)-propionamide (0.47 g, 0.96 mmol) and (S)-2-(1H-indol-3-yl)-1-carboxymethyl-ethylamine hydrochloride salt ((S)-tryptophan methyl ester hydrochloride salt) (0.28 g, 1.1 mmol). Purify by chromatography to give the title compound.

Scheme A.1, step b: (S)-N-(2-Methoxybenzyl)-N-methyl-2-[[[(S)-2-(1H-indol-3-yl)-1-carboxymethyl-ethylamino]-ethylamino]-3-(naphth-2-yl)-propionamide

Prepare by the method of Example 1, Scheme A.1, step b, using (S)-N-(2-methoxybenzyl)-N-methyl-2-[[[(S)-2-(1H-indol-3-yl)-1-carboxymethyl-ethylamino]-N'-(t-butoxycarbonyl)ethylamino]-3-(naphth-2-yl)-propionamide to

-31-

give the title compound. HRMS calculated for  $C_{32}H_{39}N_4O_4$   
543.2971. Found 543.2980.

Scheme A.1, step c: (S)-N-(2-Methoxybenzyl)-N-methyl-2-  
5 [((S)-2-(1H-indol-3-yl)-1-carboxy-ethylamino)-ethylamino]-  
3-(naphth-2-yl)-propionamide

Prepare by the method of Example 1, Scheme A.1, step c,  
using (S)-N-(2-methoxybenzyl)-N-methyl-2-[(S)-2-(1H-indol-  
3-yl)-1-carboxymethyl-ethylamino]-ethylamino-3-(naphth-2-  
10 yl)-propionamide to give the title compound.

Scheme A.1, step d: (S)-2-[(S)-3-(1H-Indol-3-ylmethyl)-2-  
oxo-piperazin-1-yl]-1-[N-methyl-N-(2-methoxybenzyl)-3-  
(naphth-2-yl)-propionamide]

15 Prepare by the method of Example 1, Scheme A.1, step d,  
using (S)-N-(2-methoxybenzyl)-N-methyl-2-[(S)-2-(1H-indol-  
3-yl)-1-carboxy-ethylamino]-ethylamino-3-(naphth-2-yl)-  
propionamide to give the title compound.

20

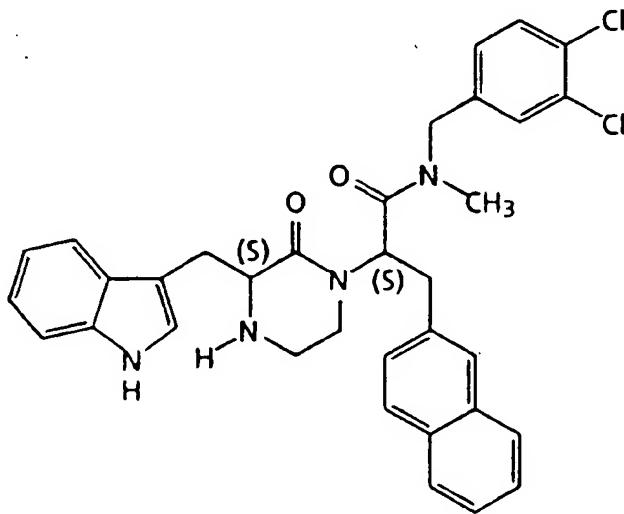
**EXAMPLE 8**

(S)-2-[(S)-3-(1H-Indol-3-ylmethyl)-2-oxo-piperazin-1-yl]-1-  
[N-methyl-N-(3,4-dichlorobenzyl)-3-(naphth-2-yl)-  
propionamide]

25

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-32-

Scheme A.1, step a: (S)-N-(3,4-Dichlorobenzyl)-N-methyl-2-  
[[(S)-2-(1H-indol-3-yl)-1-carboxymethyl-ethylamino]-N'-(t-  
butoxycarbonyl)ethylamino]-3-(naphth-2-yl)-propionamide

Prepare by the method of Example 1, Scheme A.1, step a,  
5 using (S)-N-(3,4-dichlorobenzyl)-N-methyl-2-[N'-(t-  
butoxycarbonyl)-2-oxo-ethylamino]-3-(naphth-2-yl)-  
propionamide (0.29 g, 0.55 mmol) and (S)-2-(1H-indol-3-yl)-  
1-carboxymethyl-ethylamine hydrochloride salt ((S)-  
tryptophan methyl ester hydrochloride salt) (0.14 g, 0.55  
10 mmol). Purify by chromatography eluting with 5%  
methanol/dichloromethane to give the title compound: TLC  
R<sub>f</sub>=0.58 (silica gel, 50% ethyl acetate/hexane).

Scheme A.1, step b: (S)-N-(3,4-Dichlorobenzyl)-N-methyl-2-  
15 [[(S)-2-(1H-indol-3-yl)-1-carboxymethyl-ethylamino]-  
ethylamino]-3-(naphth-2-yl)-propionamide

Prepare by the method of Example 1, Scheme A.1, step b,  
using (S)-N-(3,4-dichlorobenzyl)-N-methyl-2-[[[(S)-2-(1H-  
indol-3-yl)-1-carboxymethyl-ethylamino]-N'-(t-  
20 butoxycarbonyl)ethylamino]-3-(naphth-2-yl)-propionamide to  
give the title compound: TLC R<sub>f</sub>=0.57 (silica gel, 10%  
methanol/dichloromethane).

Scheme A.1, step c: (S)-N-(3,4-Dichlorobenzyl)-N-methyl-2-  
25 [[[(S)-2-(1H-indol-3-yl)-1-carboxy-ethylamino]-ethylamino]-  
3-(naphth-2-yl)-propionamide

Prepare by the method of Example 1, Scheme A.1, step c,  
using (S)-N-(3,4-dichlorobenzyl)-N-methyl-2-[[[(S)-2-(1H-  
indol-3-yl)-1-carboxymethyl-ethylamino]-ethylamino]-3-  
30 (naphth-2-yl)-propionamide to give the title compound.

Scheme A.1, step d: (S)-2-[(S)-3-(1H-Indol-3-ylmethyl)-2-  
oxo-piperazin-1-yl]-1-[N-methyl-N-(3,4-dichlorobenzyl)-3-  
(naphth-2-yl)-propionamide]

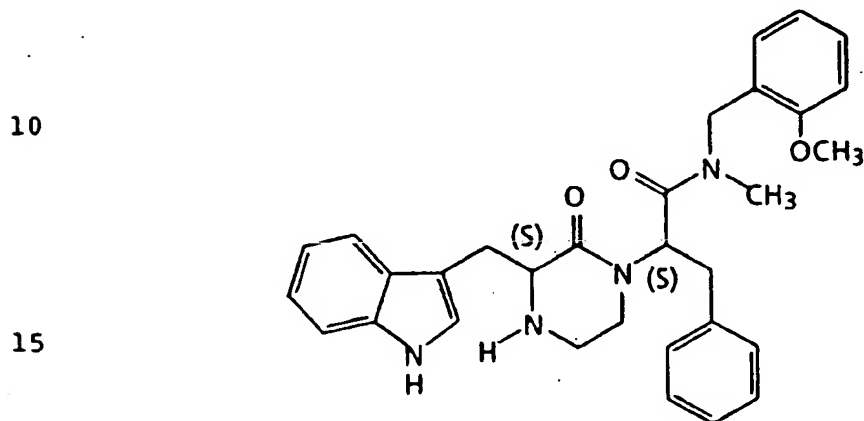
35 Prepare by the method of Example 1, Scheme A.1, step d,  
using (S)-N-(3,4-dichlorobenzyl)-N-methyl-2-[[[(S)-2-(1H-

-33-

indol-3-yl)-1-carboxy-ethylamino]-ethylamino]-3-(naphth-2-yl)-propionamide to give the title compound.

EXAMPLE 9

5 (S)-2-[(S)-3-(1H-indol-3-yl)-2-oxo-piperazin-1-yl]-1-[N-methyl-N-(2-methoxybenzyl)-3-(phenyl)-propionamide]



Scheme A, step a: (S)-N-(2-Methoxybenzyl)-N-methyl-2-[[[(S)-2-(1H-indol-3-yl)-1-carboxymethyl-ethylamino]-N'-(t-butoxycarbonyl)-ethylamino]-3-phenyl-propionamide]

20

Prepare by the method of Example 1, Scheme A.1, step a, using (S)-N-(2-methoxybenzyl)-N-methyl-2-[N'-(t-butoxycarbonyl)-2-oxo-ethylamino]-3-phenyl-propionamide (0.71 g, 1.6 mmol) and (S)-2-(1H-indol-3-yl)-1-carboxymethyl-ethylamine hydrochloride salt ((S)-tryptophan methyl ester hydrochloride salt) (0.45 g, 1.76 mmol). Purify by chromatography eluting with 50% ethyl acetate/hexane to give the title compound: TLC  $R_f$ =0.56 (silica gel, 50% ethyl acetate/hexane).

25

30

Scheme A.1, step b: (S)-N-(2-Methoxybenzyl)-N-methyl-2-[[[(S)-2-(1H-indol-3-yl)-1-carboxymethyl-ethylamino]-ethylamino]-3-phenyl-propionamide]

35

Prepare by the method of Example 1, Scheme A.1, step b, using (S)-N-(2-methoxybenzyl)-N-methyl-2-[[[(S)-2-(1H-indol-3-yl)-1-carboxymethyl-ethylamino]-N'-(t-butoxycarbonyl)-

-34-

ethylamino]-3-phenyl-propionamide to give the title compound.

Scheme A.1, step c: (S)-N-(2-Methoxybenzyl)-N-methyl-2-  
5 [((S)-2-(1H-indol-3-yl)-1-carboxy-ethylamino)--ethylamino]-  
3-phenyl-propionamide

Prepare by the method of Example 1, Scheme A.1, step c,  
using (S)-N-(2-methoxybenzyl)-N-methyl-2-[[((S)-2-(1H-indol-  
3-yl)-1-carboxymethyl-ethylamino)-ethylamino]-3-phenyl-  
10 propionamide to give the title compound.

Scheme A.1, step d: (S)-2-[(S)-3-(1H-indol-3-yl)-2-oxo-  
piperazin-1-yl]-1-[N-methyl-N-(2-methoxybenzyl)-3-(phenyl)-  
propionamide]

15 Prepare by the method of Example 1, Scheme A.1, step d,  
using (S)-N-(2-methoxybenzyl)-N-methyl-2-[[((S)-2-(1H-indol-  
3-yl)-1-carboxy-ethylamino)--ethylamino]-3-phenyl-  
propionamide to give the title compound.

20

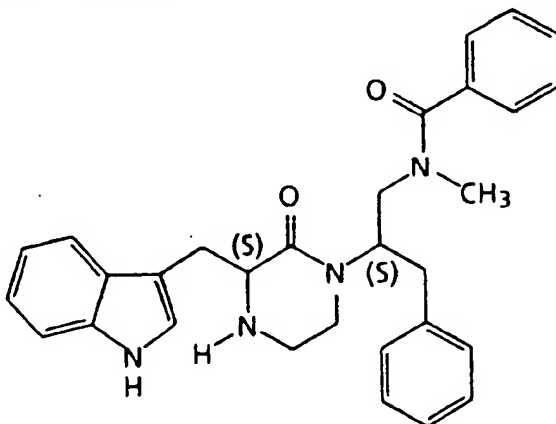
EXAMPLE 10

(S)-2-[3-(1H-Indol-3-ylmethyl)-2-oxo-piperazin-1-yl]-2-  
[[(S)-N-methyl-N-(3-phenyl-propyl)]-benzamide]

Scheme A.1 step a: N-Methyl-N-[(S)-2-[[((S)-2-(1H-indol-3-  
25 yl)-1-carboxymethyl-ethylamino)-N'-(t-butoxycarbonyl)-  
ethylamino]-3-phenyl-propyl]-benzamide

30

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-35-

Prepare by the method of Example 1, Scheme A.1, step a, using (S)-N-methyl-N-[[2-[N'-(t-butoxycarbonyl)-2-oxo-ethylamino]-3-phenylpropyl]-benzamide (0.11 g, 0.27 mmol) and (S)-2-(1H-indol-3-yl)-1-carboxymethyl-ethylamine hydrochloride salt ((S)-tryptophan methyl ester hydrochloride salt) (0.076 g, 0.3 mmol). Purify by chromatography eluting with 30% ethyl acetate/hexane to give the title compound.

10 Scheme A.1, step b: N-Methyl-N-[(S)-2-[(S)-2-(1H-indol-3-yl)-1-carboxymethyl-ethylamino]-ethylamino]-3-phenyl-propyl]-benzamide

Prepare by the method of Example 1, Scheme A.1, step b, using N-methyl-N-[(S)-2-[(S)-2-(1H-indol-3-yl)-1-carboxymethyl-ethylamino]-N'-(t-butoxycarbonyl)-ethylamino]-3-phenyl-propyl]-benzamide to give the title compound. HRMS calculated for C<sub>31</sub>H<sub>37</sub>N<sub>4</sub>O<sub>3</sub> 513.2865. Found 513.2872.

20 Scheme A.1, step c: N-Methyl-N-[(S)-2-[(S)-2-(1H-indol-3-yl)-1-carboxy-ethylamino]-ethylamino]-3-phenyl-propyl]-benzamide

Prepare by the method of Example 1, Scheme A.1, step c, using N-methyl-N-[(S)-2-[(S)-2-(1H-indol-3-yl)-1-carboxymethyl-ethylamino]-ethylamino]-3-phenyl-propyl]-benzamide to give the title compound.

30 Scheme A.1, step d: (S)-2-[3-(1H-Indol-3-ylmethyl)-2-oxo-piperazin-1-yl]-2-[(S)-N-methyl-N-(3-phenyl-propyl)]-benzamide]

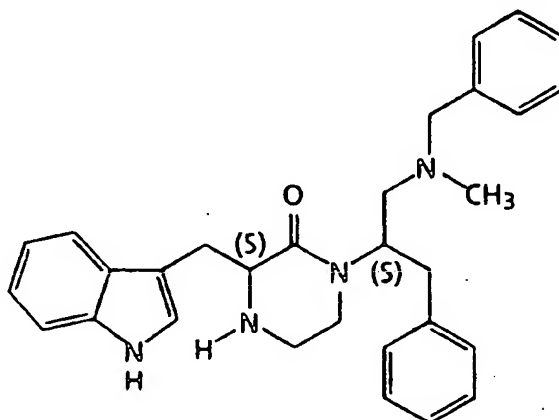
Prepare by the method of Example 1, Scheme A.1; step d, using N-methyl-N-[(S)-2-[(S)-2-(1H-indol-3-yl)-1-carboxy-ethylamino]-ethylamino]-3-phenyl-propyl]-benzamide to give the title compound.

Example 12

5 (S)-2-[3-(1H-Indol-3-ylmethyl)-2-oxo-piperazin-1-yl]-[(S)-  
N-methyl-N-benzyl-3-(phenyl)-propylamine]

10

15



20

Scheme A.1, step a: N-Methyl-N-benzyl-N-[(S)-2-[(S)-2-(1H-  
indol-3-yl)-1-carboxymethyl-ethylamino]-N'-(t-  
butoxycarbonyl)-ethylamino]-3-phenyl-propylamine

25

Prepare by the method of Example 1, Scheme A.1, step a, using (S)-N-methyl-N-benzyl-N-[2-[N'-(t-butoxycarbonyl)-2-oxo-ethylamino]-3-phenyl-propylamine (0.5 mmol) and (S)-2-(1H-indol-3-yl)-1-(carboxymethyl-ethylamine hydrochloride salt ((S)-tryptophan methyl ester hydrochloride salt) (0.55 mmol). Purify by chromatography to give the title compound.

30

Scheme A.1, step b: N-Methyl-N-benzyl-N-[(S)-2-[(S)-2-(1H-  
indol-3-yl)-1-carboxymethyl-ethylamino]-ethylamino]-3-  
phenyl-propylamine

35

Prepare by the method of Example 1, Scheme A.1, step b, using N-methyl-N-benzyl-N-[(S)-2-[(S)-2-(1H-indol-3-yl)-1-carboxymethyl-ethylamino]-N'-(t-butoxycarbonyl)-ethylamino]-3-phenyl-propylamine to give the title compound.

-37-

Scheme A.1, step c: N-Methyl-N-benzyl-N-[(S)-2-[(S)-2-(1H-indol-3-yl)-1-carboxy-ethylamino]-ethylamino]-3-phenyl-propylamine

5 Prepare by the method of Example 1, Scheme A.1, step c, using N-methyl-N-benzyl-N-[(S)-2-[(S)-2-(1H-indol-3-yl)-1-carboxymethyl-ethylamino]-ethylamino]-3-phenyl-propylamine to give the title compound.

Scheme A.1, step d: (S)-2-[3-(1H-Indol-3-ylmethyl)-2-oxo-piperazin-1-yl]-[(S)-N-methyl-N-benzyl-3-(phenyl)-propylamine]

10 Prepare by the method of Example 1, Scheme A.1, step d, using N-methyl-N-benzyl-N-[(S)-2-[(S)-2-(1H-indol-3-yl)-1-carboxy-ethylamino]-ethylamino]-3-phenyl-propylamine to  
15 give the title compound.

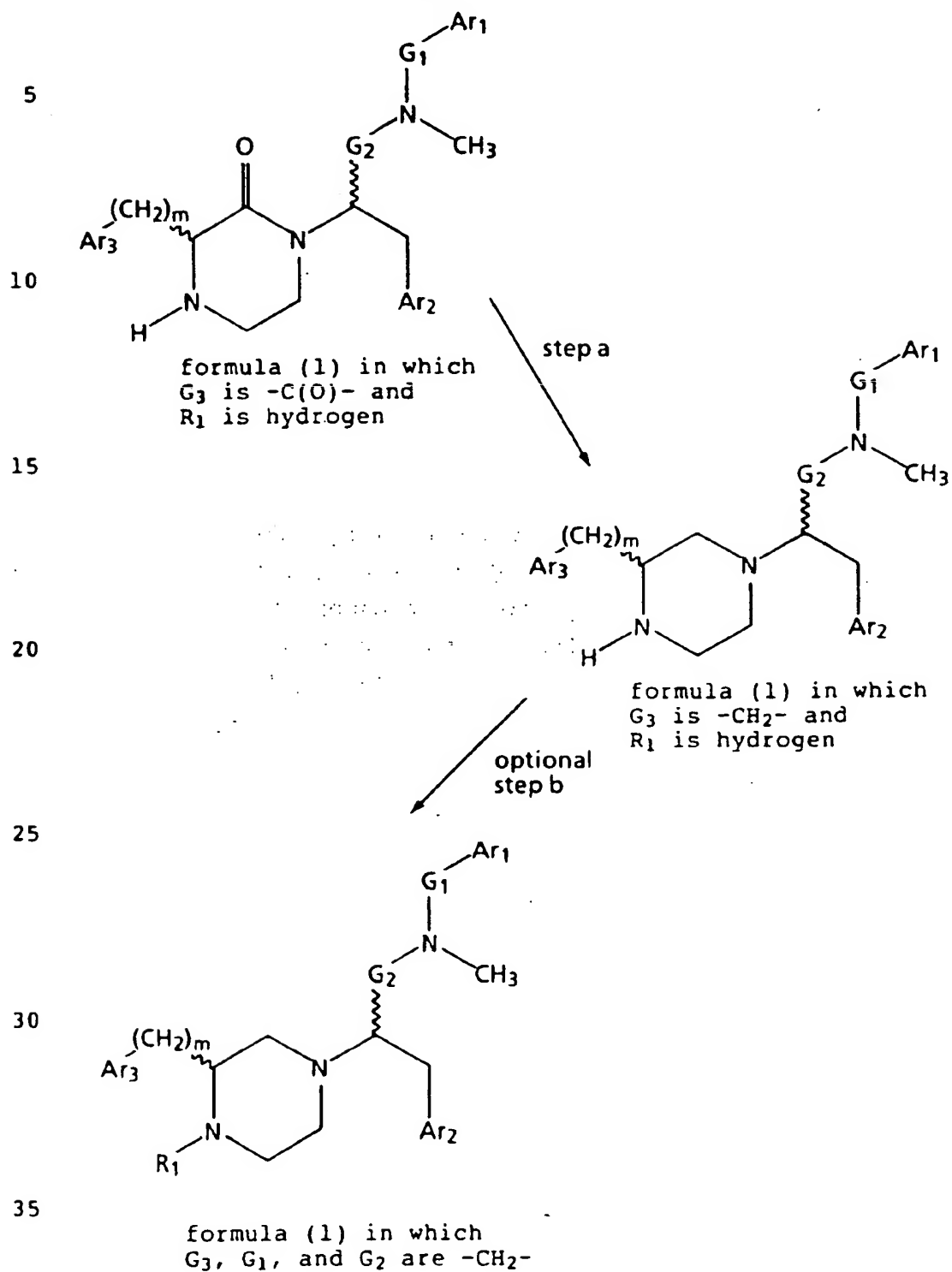
A general synthetic procedure for preparing these compounds of formula (1) in which G<sub>3</sub> is -CH<sub>2</sub>- is set forth in Scheme A.2. The reagents and starting materials are  
20 readily available to one of ordinary skill in the art. In Scheme A.2, all substituents, unless otherwise indicated, are as previously defined.

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**Scheme A.2**



-39-

In Scheme A.2, step a, an appropriate compound of formula (1) in which  $G_3$  is  $-C(O)-$  and  $R_1$  is hydrogen is reduced to give a compound of formula (1) in which  $G_3$  is  $-CH_2-$  and  $R_1$  is hydrogen.

5

For Scheme A.2, an appropriate compound of formula (1) is one in which  $G_1$  and  $G_2$  are either  $-C(O)-$  or  $-CH_2-$ ,  $G_3$  is  $-C(O)-$  and  $R_1$  is hydrogen; and stereochemistry,  $m$ ,  $Ar_1$ ,  $Ar_2$ , and  $Ar_3$  are as desired in the final product of formula (1) or can also be one in which the stereochemistry and  $Ar_1$ ,  $Ar_2$ , and  $Ar_3$  give rise after resolution, deprotection, or modification to stereochemistry and  $Ar_1$ ,  $Ar_2$ , and  $Ar_3$  as desired in the final product of formula (1).

15 For example, an appropriate compound of formula (1) is contacted with a from 1 to 10 equivalents of a suitable amide reducing agent, such as lithium aluminum hydride, diisobutylaluminum hydride, or borane dimethyl sulfide complex. The amount of suitable amide reducing agent used  
20 depends on the number of amides reduced in Scheme A.2, step a, for example, when either  $G_1$  or  $G_2$  are  $-C(O)-$  the amount of amide reducing agent used will be increased as is well known and appreciated in the art. The reaction is carried out in a suitable solvent, such as tetrahydrofuran,  
25 toluene, or diethyl ether. Generally, the reaction is carried out at temperatures of from  $0^\circ C$  to the refluxing temperature of the solvent. Generally, the reactions require from 1 to 72 hours. The product can be isolated and purified by techniques well known in the art, such as  
30 quenching, extraction, evaporation, chromatography, and recrystallization.

In Scheme A.2, optional step b, a protected compound of formula (1) may be deprotected or modified to give a  
35 compound of formula (1) as generally taught above in Scheme A.1, optional step f.

-40-

The following examples present typical syntheses as described in Scheme A.2. These examples are understood to be illustrative only and are not intended to limit the scope of the invention in any way.

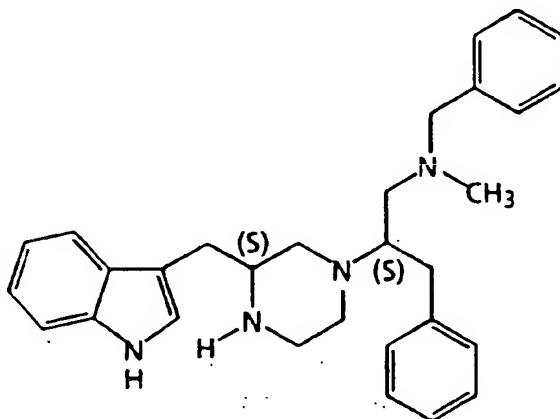
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EXAMPLE 13

(S)-2-[(S)-3-(1H-Indol-3-ylmethyl)-piperazin-1-yl]-[N-methyl-N-benzyl-3-(phenyl)-propylamine]

10

15



20 Scheme A.2, step a: (S)-2-[(S)-3-(1H-Indol-3-ylmethyl)-piperazin-1-yl]-[N-methyl-N-benzyl-3-(phenyl)-propylamine]

Combine (S)-2-[(S)-3-(1H-Indol-3-ylmethyl)-2-oxo-piperazin-1-yl]-1-[N-methyl-N-benzyl-3-(phenyl)-propionamide] (5 mmol) and tetrahydrofuran (25 mL).

25 Slowly add portionwise lithium aluminum hydride (16 mmol). Heat to reflux for 48 hours. Cool to ambient temperature, slowly add water (0.6 mL), 15% sodium hydroxide solution (0.6 mL), and water (1.8 mL). Stir until all the reducing reagent is quenched. Filter and evaporate *in vacuo* to obtain  
30 a residue. Partition the residue between ethyl acetate and water. Separate the organic layer and dry over MgSO<sub>4</sub>, filter, and evaporate *in vacuo* to give the title compound.

A general synthetic procedure is set forth in Scheme B  
35 for preparing the aldehyde of structure (3), in which G<sub>1</sub> is -CH<sub>2</sub>- and G<sub>2</sub> is -C(O)-, used as a starting material in Scheme A.1. The reagents and starting materials are

-41-

readily available to one of ordinary skill in the art. In Scheme B, all substituents, unless otherwise indicated, are as previously defined.

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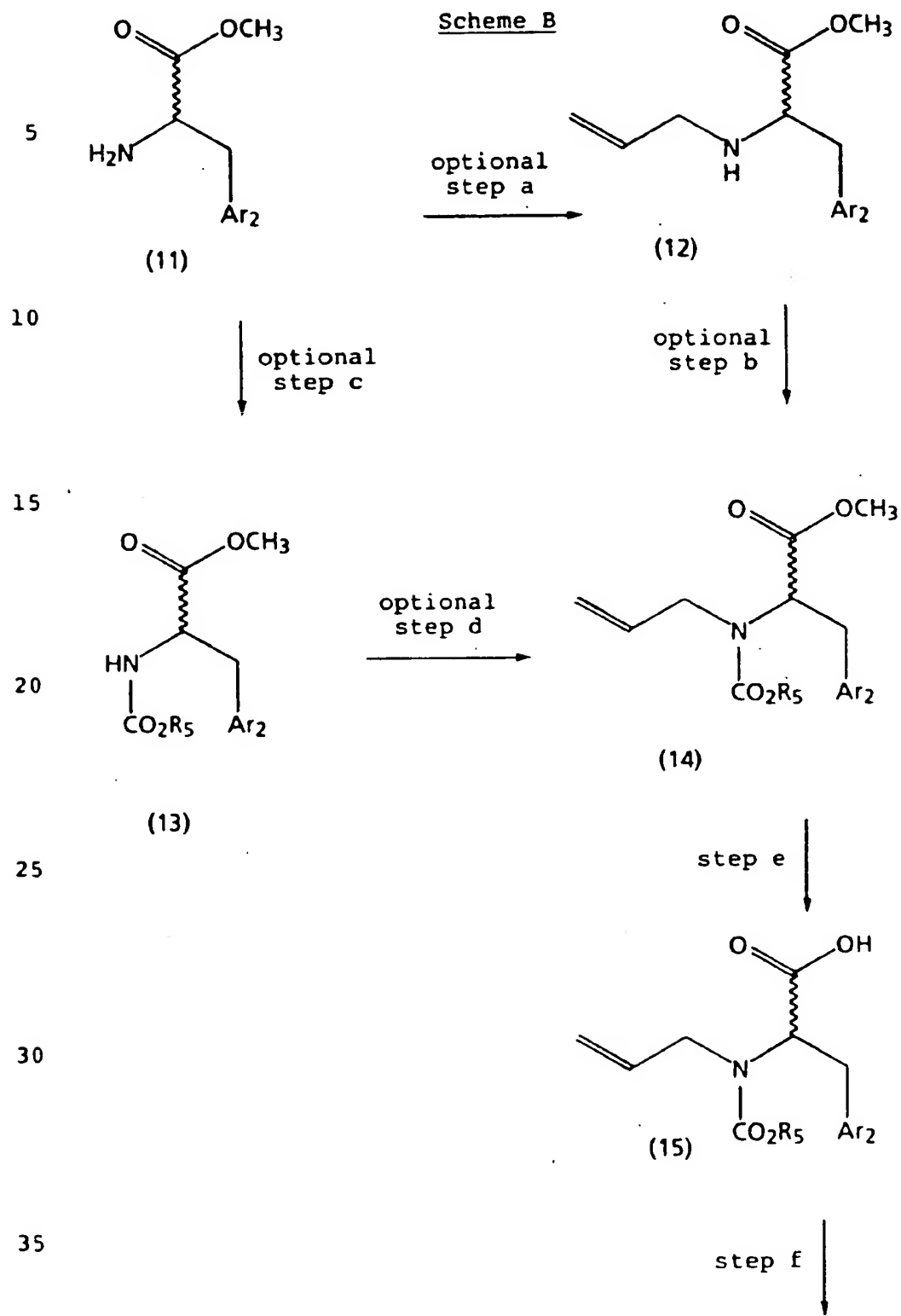
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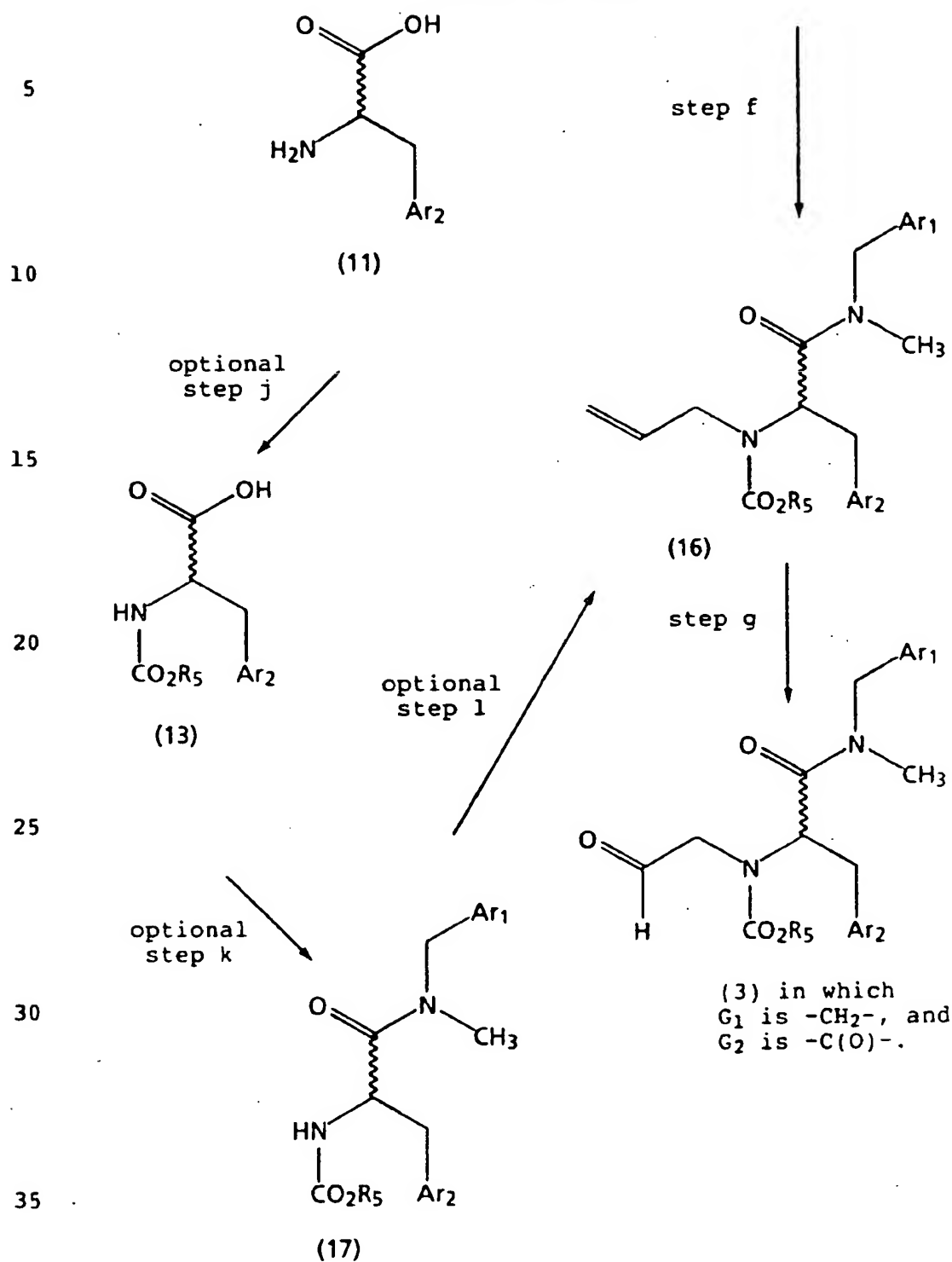
-42-

## Scheme B





## Scheme B Cont.



-44-

In Scheme B, optional step a, an appropriate amino ester of structure (11) or a salt thereof is allylated to give an allylamino ester of structure (12).

5        An appropriate amino ester of structure (11) or a salt of thereof is one in which the stereochemistry and  $Ar_2$  are as desired in the product of formula (1) or can be one which gives rise after resolution or deprotection to stereochemistry or  $Ar_2$  as desired in the final product of  
10    formula (1).

For example, an appropriate amino ester of structure (11) or a salt of an appropriate amino ester of structure (11) is contacted with from 1 to 3 molar equivalents of  
15    allyl bromide or allyl chloride. The allyl bromide or allyl chloride is preferably added portionwise over the course of the reaction. When a salt of an appropriate amino ester of structure (11) is used the reaction is carried out in the presence of an equimolar amount of a  
20    suitable base, such as triethyl amine or diisopropylethyl amine. The reaction is carried out in a suitable solvent, such as tetrahydrofuran. Generally, the reaction is carried out at temperatures of from 0°C to 60°C. Generally, the reactions require from 1 to 72 hours. The  
25    product can be isolated and purified by techniques well known in the art, such as extraction, evaporation, chromatography, and recrystallization.

In Scheme B, optional step b, an allylamino ester of  
30    structure (12) or as salt thereof the allyl amino group is converted to a carbamate with an appropriate carbamate forming reagent to give a compound of structure (14).

An appropriate carbamate forming reagent is one which  
35    transfers to an amine the group  $-CO_2R_5$ , such as methyl chloroformate, ethyl chloroformate, propyl chloroformate, iso-butyl chloroformate, and di-t-butyl dicarbonate, etc.

For example, an allylamino ester of structure (12) or as salt thereof is contacted with a reagent which transfers to an amine the group  $-CO_2R_5$ . When a salt of an allylamino ester of structure (12) is used the reaction is carried out in the presence of an equimolar amount of a suitable base, such as triethylamine or diisopropylethylamine. When the reaction is carried out using a carbamate forming reagent which liberates acid as the carbamate is formed, such as methyl chloroformate, ethyl chloroformate, propyl chloroformate, iso-butyl chloroformate, etc, an equimolar amount of a suitable base, such as triethylamine or diisopropylethylamine is used to neutralize the acid which is liberated. The reaction is carried out in a suitable solvent, such as tetrahydrofuran, dimethylformamide, ethyl acetate, or dimethylformamide/ethyl acetate mixtures. Generally, the reactions are carried out at ambient temperature. The product can be isolated and purified by techniques well known in the art, such as extraction, evaporation, chromatography, and recrystallization.

Alternately, a carbamate of structure (14) in which  $R_5$  is t-butyl may be prepared by Scheme B, optional steps c and d.

25

In Scheme B, optional step c, an appropriate amino ester of structure (11) or a salt thereof is contacted with an appropriate carbamate forming reagent to give a compound of structure (13).

30

An appropriate carbamate forming reagent for the use of this alternate route for preparing compounds of structure (14) is one which transfers an t-butyl carbamate, such as di-t-butyl dicarbonate.

35

An appropriate amino ester of structure (11) or a salt thereof is one in which the stereochemistry and  $Ar_2$  are as

-46-

desired in the product of formula (1) or can be one which gives rise after resolution or deprotection to stereochemistry or Ar<sub>2</sub> as desired in the final product of formula (1).

5

For example, an amino ester of structure (11) or as salt thereof is contacted with a reagent which transfers a t-butoxycarbonyl group, such as di-t-butyl dicarbonate. When a salt of an amino ester of structure (11) is used the reaction is carried out in the presence of an equimolar amount of a suitable base, such as triethyl amine or diisopropylethyl amine. The reaction is carried out in a suitable solvent, such as dimethylformamide, ethyl acetate, or dimethylformamide/ethyl acetate mixtures. Generally, the reactions are carried out at ambient temperature. The product can be isolated and purified by techniques well known in the art, such as extraction, evaporation, chromatography, and recrystallization.

20

In Scheme B, optional step d, a carbamate ester of structure (13) in which R<sub>5</sub> is t-butyl is allylated to give an allyl-carbamate ester of structure (14) in which R<sub>5</sub> is t-butyl.

25

For example, a carbamate ester of structure (13) is contacted with allyl bromide or allyl chloride. The reaction is carried out in the presence of a suitable base, such as sodium hydride. The reaction is carried out in a suitable solvent, such as tetrahydrofuran, dimethylformamide, or tetrahydrofuran/dimethylformamide mixtures. The reaction is carried out at temperature of from 0°C to the reflux temperature of the solvent. The product can be isolated and purified by techniques well known in the art, such as extraction, evaporation, chromatography, and recrystallization.

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-47-

In Scheme B, step e, an allyl-carbamate ester of structure (14) is hydrolyzed to give an allyl-carbamate acid of structure (15).

5 For example, an allyl-carbamate ester of structure (14) is contacted with a suitable base, such as sodium hydroxide, lithium hydroxide, or potassium hydroxide. The reaction is carried out in a suitable solvent, such as methanol, ethanol, water, methanol/water mixtures,  
10 ethanol/water mixtures, or tetrahydrofuran/water mixtures. Generally, the reaction is carried out at ambient temperature. Generally, the reaction requires from 2 to 72 hours. The product can be isolated and purified by techniques well known in the art, such as acidification,  
15 filtration, extraction, evaporation, and recrystallization.

In Scheme B, step f, an allyl-carbamate acid of structure (15) undergoes an amidation reaction with an appropriate amine to give an allyl-carbamate amide of  
20 structure (16).

An appropriate amine of structure  $\text{HN}(\text{CH}_3)\text{CH}_2\text{Ar}_1$  is one in which the group  $\text{Ar}_1$  is as desired in the product of formula (1) or give rise after deprotection to  $\text{Ar}_1$  as  
25 desired in the final product of formula (1).

An amidation reaction may proceed through an activated intermediate, such as a mixed anhydride or a (O)-hydroxybenzotriazole, which may be prepared but is not  
30 necessarily isolated before the addition of an appropriate amine,  $\text{HN}(\text{CH}_3)\text{CH}_2\text{Ar}_1$ .

For example, an allyl-carbamate acid of structure (15) is contacted with 1.2 to 1.7 equivalents of a suitable  
35 base, such as N-methylmorpholine, in a suitable solvent, such as tetrahydrofuran. Generally, the reaction mixture is cooled to a temperature of between  $-50^\circ\text{C}$  and  $0^\circ\text{C}$  with

-48-

-25°C to -20°C being preferred, before the addition of 1.2 to 1.7 equivalents of isobutyl chloroformate. The reaction is allowed to stir for about 30 minutes to 3 hours to allow for the formation of the mixed anhydride, an activated  
5 intermediate. While maintaining the temperature at between -50°C and 0°C an appropriate amine of structure  $\text{HN}(\text{CH}_3)\text{CH}_2\text{Ar}_1$  is added. The reaction may, after the addition of amine is complete, be warmed to room temperature. The reaction requires from 2 to 48 hours.  
10 The product can be isolated and purified by techniques well known in the art, such as extraction, evaporation, chromatography, and recrystallization.

Alternatively, for example, an allyl-carbamate acid of  
15 structure (15) is contacted with a slight molar excess of an appropriate amine,  $\text{HN}(\text{CH}_3)\text{CH}_2\text{Ar}_1$ , and 1-hydroxybenzotriazole hydrate in the presence of a slight molar excess of a coupling agent, such as dicyclohexylcarbodiimide or 1-(3-dimethylaminopropyl)-3-  
20 ethylcarbodiimide. The reaction is carried out in the presence of a suitable base, such as diisopropylethylamine. The reaction is carried out in a suitable solvent, such as dimethylformamide, dichloromethane, or chloroform. The product can be isolated and purified by techniques well  
25 known in the art, such as extraction, evaporation, chromatography, and recrystallization.

Alternately, an allyl-carbamate amide of structure (16) can be prepared from an amino acid according to Scheme B  
30 optional steps j, k, and l.

In Scheme B, optional step j, an appropriate amino acid of structure (11) or a salt thereof is contacted with an appropriate carbamate forming reagent to give a compound of  
35 structure (17).

-49-

An appropriate carbamate forming reagent for the use of this alternate route for preparing compounds of structure (13) is one which transfers a t-butyl carbamate, such as di-t-butyl dicarbonate.

5

An appropriate amino acid of structure (11) or a salt thereof is one in which the stereochemistry and  $Ar_2$  are as desired in the product of formula (1) or is one which gives rise after resolution or deprotection to stereochemistry or  
10  $Ar_2$  as desired in the final product of formula (1).

For example, an appropriate amino acid of structure (11) or a salt thereof is contacted with a reagent which transfers a t-butoxycarbonyl group, such as di-t-butyl  
15 dicarbonate. The reaction is carried out in the presence of an equimolar amount of a suitable base, such as triethyl amine or diisopropylethyl amine. When a salt of an appropriate amino acid of structure (11) is used an additional equimolar amount of a suitable base is used.  
20 The reaction is carried out in a suitable solvent, such as dimethylformamide, ethyl acetate, or dimethylformamide/ethyl acetate mixtures. Generally, the reactions are carried out at ambient temperature. The product can be isolated and purified by techniques well  
25 known in the art, such as extraction, evaporation, chromatography, and recrystallization.

In Scheme B, step k, a t-BOC protected amino acid of structure (13) undergoes an amidation reaction with an  
30 appropriate amine, as generally taught in Scheme B, step f, to give a t-BOC protected amino amide of structure (17).

An appropriate amine of structure  $HN(CH_3)CH_2Ar_1$  is one in which  $Ar_1$  is as desired in the product of formula (1) or  
35 give rise after deprotection to  $Ar_1$  as desired in the final product of formula (1).

-50-

In Scheme B, optional step 1, a t-BOC protected amino amide of structure (17) is allylated as generally taught in Scheme B, optional step d, to give an allyl-carbamate amide of structure (16) in which R<sub>5</sub> is t-butyl.

5

In Scheme B, step g, an allyl-carbamate amide of structure (16) is converted to an aldehyde of structure (3). An allyl-carbamate amide of structure (16) may be converted to an aldehyde of structure (3) by either;  
10 ozonolysis in the presence of methanol followed by a reductive work-up, or an osmium tetroxide mediated formation of an intermediate diol followed by oxidative cleavage with lead tetraacetate or sodium meta-periodate.

15

The following examples present typical syntheses as described in Scheme B. These examples and preparations are understood to be illustrative only and are not intended to limit the scope of the invention in any way.

20

#### EXAMPLE 44

##### 2-(Methoxy)benzylmethylamine

##### Starting material for Examples 50 and 55;

Combine o-anisoyl chloride (2-methoxybenzoyl chloride)  
25 (2.9 g, 17.0 mmol) and tetrahydrofuran (170 mL) and cool to 0°C. Add diisopropylethylamine (5.92 mL, 34 mmol). Add methylamine hydrochloride (1.26 g, 18.7 mmol). Allow to stir for 1 hour and concentrate *in vacuo*. Chromatograph on silica gel eluting sequentially with 50% ethyl  
30 acetate/hexane to give N-methyl-2-methoxybenzamide: TLC R<sub>f</sub>=0.45 (silica gel, 50% ethyl acetate/hexane).

Combine N-methyl-2-methoxybenzamide (1.55 g, 9.36 mmol) and tetrahydrofuran (100 mL) and heat to reflux. Slowly,  
35 add dropwise a solution of borane dimethyl sulfide complex (28.1 mL, 2.0M in tetrahydrofuran, 56.2 mmol). Heat to reflux for 1 hour after the addition is complete. Cool to



-51-

ambient temperature and concentrate *in vacuo* to obtain a residue. Cool the residue to 0°C. Slowly, add 6M hydrochloric acid solution. After the addition is complete, heat the mixture to reflux for 1 hour. Cool to 0°C, add 6M sodium hydroxide solution until the pH is 7. Extract the reaction mixture with ethyl acetate. Dry the organic layer over MgSO<sub>4</sub>, filter, and evaporate *in vacuo* to give the title compound.

10

EXAMPLE 453,4,5-(Trimethoxy)benzylmethanamineStarting material for Example 51;

Combine 3,4,5-trimethoxybenzoyl chloride) (2.9 g, 17.0 mmol) and tetrahydrofuran (170 mL) and cool to 0°C. Add diisopropylethylamine (5.92 mL, 34 mmol). Add methanamine hydrochloride (1.26 g, 18.7 mmol). Allow to stir for 1 hour and concentrate *in vacuo*. Chromatograph on silica gel eluting sequentially with 50% ethyl acetate/hexane to give N-methyl-3,4,5-trimethoxybenzamide: TLC R<sub>f</sub>=0.45 (silica gel, 50% ethyl acetate/hexane).

Combine N-methyl-3,4,5-trimethoxybenzamide (1.55 g, 9.36 mmol) and tetrahydrofuran (100 mL) and heat to reflux. Slowly, add dropwise a solution of borane dimethyl sulfide complex (28.1 mL, 2.0M in tetrahydrofuran, 56.2 mmol). Heat to reflux for 1 hour after the addition is complete. Cool to ambient temperature and concentrate *in vacuo* to obtain a residue. Cool the residue to 0°C. Slowly, add 6M hydrochloric acid solution. After the addition is complete, heat the mixture to reflux for 1 hour. Cool to 0°C, add 6M sodium hydroxide solution until the pH is 7. Extract the reaction mixture with ethyl acetate. Dry the organic layer over MgSO<sub>4</sub>, filter, and evaporate *in vacuo* to give the title compound.

35

EXAMPLE 46(S)-2-Allylamin-3-phenyl-propionic acid methyl ester

-52-

Scheme B, optional step a:

Combine (S)-2-amino-3-phenyl-propionic acid methyl ester hydrochloride salt ((S)-phenylalanine methyl ester hydrochloride salt) (8.63 g, 40.0 mmol),  
5 diisopropylethylamine (6.8 mL, 40.0 mmol), and allyl bromide (1.8 mL, 20.0 mmol) in THF (200 mL). Stir under an inert atmosphere for 16 hours. Add allyl bromide (1.8 mL, 20.0 mmol) and stir for an additional 24 hours. Concentrate *in vacuo* to obtain a residue. Dilute the residue  
10 with ethyl acetate and extract with water. Separate the layers, dry the organic layer over MgSO<sub>4</sub>, filter, and evaporate *in vacuo*. Chromatograph on silica gel eluting with 30% ethyl acetate/hexane to give the title compound: TLC R<sub>f</sub>=0.43 (silica gel, 30% ethyl acetate/hexane).

15

EXAMPLE 47

(S)-2-[N-(t-Butoxycarbonyl)-allylamino]-3-phenyl-propionic acid methyl ester

Scheme B, optional step b:

20 Combine (S)-2-allylamino-3-phenyl-propionic acid methyl ester (6.62g, 30.4 mmol) and di-t-butyl dicarbonate (7.29 g, 33.5 mmol) in DMF/ethyl acetate (30 mL/30 mL). Stir for 16 hours under an inert atmosphere. Dilute the reaction mixture with ethyl acetate and extract with water.  
25 Separate the layers, dry the organic layer over MgSO<sub>4</sub>, filter, and evaporate *in vacuo*. Chromatograph on silica gel eluting with 10% ethyl acetate/hexane to give the title compound.

30

EXAMPLE 48

(S)-2-[N-(t-Butoxycarbonyl)-allylamino]-3-phenyl-propionic acid

Scheme B, step e:

Combine (S)-2-[N-(t-butoxycarbonyl)-allylamino]-3-phenyl-propionic acid methyl ester (0.32 g, 1.0 mmol) and  
35 1M sodium hydroxide (10 mL, 10 mmol) in ethanol (10 mL). Stir for 4 hours. Acidify the reaction mixture with 1M

-53-

hydrochloric acid and extract with ethyl acetate. Separate the layers, dry the organic layer over  $\text{MgSO}_4$ , filter, and evaporate *in vacuo*. Chromatograph on silica gel eluting with 3% methanol/dichloromethane to give the title compound: TLC  
5  $R_f=0.40$  (silica gel, 5% methanol/dichloromethane).

EXAMPLE 49(S)-N-Benzyl-N-methyl-2-[N-(t-butoxycarbonyl)-allylamino]-3-phenyl-propionamide10 Scheme B, step f:

Combine (S)-2-[N-(t-butoxycarbonyl)-allylamino]-3-phenyl-propionic acid (11.1 g, 36.35 mmol), and THF (360 mL). Cool to  $-22^\circ\text{C}$ . Add N-methylmorpholine (7.09 mL, 54.53 mmol) and then stir for 10 minutes. Add isobutyl  
15 chloroformate (7.09 mL, 54.53 mmol) and stir for 30 minutes at  $-22^\circ\text{C}$ . Add N-methyl-N-benzylamine (7.09 mL, 54.53 mmol). Allow to warm to ambient temperature and stir for 2 hours. Dilute the reaction mixture with ethyl acetate and extract with water. Separate the layers, dry  
20 the organic layer over  $\text{MgSO}_4$ , filter, and evaporate *in vacuo*. Chromatograph on silica gel eluting with 10% ethyl acetate/hexane to give the title compound.

EXAMPLE 5025 (S)-N-(2-Methoxybenzyl)-N-methyl-2-[N'-(t-butoxycarbonyl)-allylamino]-3-phenyl-propionamideScheme B, step g:

Combine (S)-2-[N-(t-butoxycarbonyl)-allylamino]-3-phenyl-propionic acid (1.59 g, 5.20 mmol), (2-methoxy-  
30 benzyl)methylamine (0.79 g, 5.20 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.12 g, 5.72 mmol), 1-hydroxybenzotriazole (0.38 g, 2.52 mmol), and diisopropylethylamine (1.34 mL, 6.5 mmol) in dichloromethane (50 mL) and stir for 18 hours. Dilute with  
35 ethyl acetate and extract with 1M hydrochloric acid, a saturated aqueous solution of sodium bicarbonate and a saturated aqueous solution of sodium chloride. Dry the

-54-

separated organic layer over  $\text{MgSO}_4$ , filter and evaporate *in vacuo*. Chromatograph on silica gel eluting sequentially with 5% ethyl acetate/hexane and 10% ethyl acetate/hexane to give the title compound: TLC  $R_f=0.55$  (silica gel, 30% ethyl acetate/hexane).

#### EXAMPLE 51

(S)-N-(3,4,5-Trimethoxybenzyl)-N-methyl-2-[N'-(t-butoxycarbonyl)-allylamino]-3-phenyl-propionamide

10 Scheme B, step g:

Combine (S)-2-[N-(t-butoxycarbonyl)-allylamino]-3-phenyl-propionic acid (0.91 g, 2.97 mmol), (3,4,5-trimethoxy)-benzylmethylamine (0.63 g, 2.97 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.63 g, 3.27 mmol), 1-hydroxybenzotriazole (0.349 g, 3.27 mmol), and diisopropylethylamine (0.77 mL, 6.27 mmol) in dichloromethane (30 mL) and stir for 18 hours. Dilute with ethyl acetate and extract with 1M hydrochloric acid, a saturated aqueous solution of sodium bicarbonate and a saturated aqueous solution of sodium chloride. Dry the separated organic layer over  $\text{MgSO}_4$ , filter and evaporate *in vacuo*. Chromatograph on silica gel eluting sequentially with 10% methanol/dichloromethane and 30% methanol/dichloromethane to give the title compound: TLC  $R_f=0.30$  (silica gel, 30% ethyl acetate/hexane)

#### EXAMPLE 52

(S)-2-[N-(t-Butoxycarbonyl)amino]-3-(naphth-2-yl)-propionic acid

30 Scheme B, optional step i:

Combine (S)-2-amino-3-(naphth-2-yl)-propionic acid ((S)-(2-naphthyl)-alanine) (2.0 g, 9.29 mmol) and di-t-butyl dicarbonate (2.23 g, 10.22 mmol) in 1/1 DMF/ethyl acetate (200 mL). Add diisopropylethylamine (2.0 mL) to solubilized the (S)-2-amino-3-(2-naphthyl)-propionic acid and stir for 18 hours. Dilute with ethyl acetate and extract with 1M hydrochloric acid solution. Dry the

-55-

separated organic layer over  $\text{MgSO}_4$ , filter and evaporate *in vacuo* to give the title compound: TLC  $R_f=0.47$  (silica gel, 10% methanol/dichloromethane).

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EXAMPLE 53

(S)-N-Benzyl-N-methyl-2-[N'-(t-butoxycarbonyl)amino]-3-(naphth-2-yl)-propionamide

5 Scheme B, optional step k:

Combine (S)-2-[N-(t-butoxycarbonyl)amino]-3-(naphth-2-yl)-propionic acid (2.92 g, 9.3 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.96 g, 10.22 mmol), 1-hydroxybenzotriazole (1.38 g, 10.22  
10 mmol), N-methyl-N-benzylamine (9.3 mmol), and diisopropylethylamine (1.78 mL, 10.22 mmol) in dichloromethane (100 mL) and stir for 18 hours. Dilute with ethyl acetate and extract with 1M hydrochloric acid, a saturated aqueous solution of sodium bicarbonate and a  
15 saturated aqueous solution of sodium chloride. Dry the separated organic layer over MgSO<sub>4</sub>, filter and evaporate *in vacuo*. Chromatograph on silica gel eluting with 20% ethyl acetate/hexane to give the title compound: TLC R<sub>f</sub>=0.29 (silica gel, 20% ethyl acetate/hexane).

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EXAMPLE 54

(S)-N-(3,4-Dichlorobenzyl)-N-methyl-2-[N'-(t-butoxycarbonyl)amino]-3-(naphth-2-yl)-propionamide

Scheme B, optional step k:

25 Combine (S)-2-[N-(t-butoxycarbonyl)amino]-3-(naphth-2-yl)-propionic acid (1.23 g, 3.93 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.435 g, 2.2 mmol), 1-hydroxybenzotriazole (0.297 g, 2.2 mmol), N-methyl-N-(3,4-dichlorobenzyl)amine (0.382, 2.0  
30 mmol), and diisopropylethylamine (0.53 mL, 2.2 mmol) in dichloromethane (20 mL) and stir for 72 hours. Dilute with ethyl acetate and extract with 1M hydrochloric acid, a saturated aqueous solution of sodium bicarbonate and a saturated aqueous solution of sodium chloride. Dry the  
35 separated organic layer over MgSO<sub>4</sub>, filter and evaporate *in vacuo*. Chromatograph on silica gel eluting with 10% ethyl acetate/hexane to give the title compound.

-57-

EXAMPLE 55

(S)-N-(2-Methoxybenzyl)-N-methyl-2-[N'-(t-butoxycarbonyl)amino]-3-(naphth-2-yl)-propionamide

5 Scheme B, optional step k:

Combine (S)-2-[N-(t-butoxycarbonyl)amino]-3-(naphth-2-yl)-propionic acid (1.89 g, 6.0 mmol), (2-methoxybenzyl)methylamine (1.67 g, 11.1 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride  
10 (1.30 g, 6.6 mmol), 1-hydroxybenzotriazole (0.89 g, 6.6 mmol), and diisopropylethylamine (1.59 mL, 6.6 mmol) in dichloromethane (60 mL) and stir for 18 hours. Dilute with ethyl acetate and extract with 1M hydrochloric acid, a saturated aqueous solution of sodium bicarbonate and a  
15 saturated aqueous solution of sodium chloride. Dry the separated organic layer over MgSO<sub>4</sub>, filter and evaporate *in vacuo* to give the title compound as a colorless oil.

EXAMPLE 56

20 (S)-N-Benzyl-N-methyl-2-[N'-(t-butoxycarbonyl)-allylamino]-3-(naphth-2-yl)-propionamide

Scheme B, optional step l:

Combine (S)-N-benzyl-N-methyl-2-[N'-(t-butoxycarbonyl)amino]-3-(naphth-2-yl)-propionamide (3.3 g,  
25 7.9 mmol) and THF/DMF (70 mL/7 mL) and cool in an ice bath at 0°C. Add sodium hydride (0.7 g, 60% in oil, 17.38 mmol) and allyl bromide (4.1 mL, 47.4 mmol). Allow the reaction to warm to ambient temperature and then heat to reflux for 18 hours. Pour the reaction mixture into a saturated  
30 aqueous solution of ammonium chloride. Separate the layers and extract the aqueous layer with dichloromethane. Combine the organic layers. Dry over MgSO<sub>4</sub>, filter, and evaporate *in vacuo*. Chromatograph on silica gel eluting sequentially with 10% ethyl acetate/hexane and 20% ethyl  
35 acetate/hexane to give the title compound: TLC R<sub>f</sub>=0.59 (silica gel, 20% ethyl acetate/hexane).

-58-

EXAMPLE 57

(S)-N-(3,4-Dichlorobenzyl)-N-methyl-2-[N'-(t-butoxycarbonyl)-allylamino]-3-(naphth-2-yl)-propionamide

5 Scheme B, optional step 1:

Combine (S)-N-(3,4-dichlorobenzyl)-N-methyl-2-[N'-(t-butoxycarbonyl)amino]-3-(naphth-2-yl)-propionamide (0.48 g, 0.99 mmol) and THF/DMF (9 mL/1 mL) and cool in an ice bath at 0°C. Add sodium hydride (0.048 g, 60% in oil, 2.0 mmol) and allyl bromide (0.52 mL). Allow the reaction to warm to ambient temperature and then heat to reflux for 18 hours. Pour the reaction mixture into a saturated aqueous solution of ammonium chloride. Separate the layers and extract the aqueous layer with dichloromethane. Combine the organic layers. Dry over MgSO<sub>4</sub>, filter, and evaporate *in vacuo*. Chromatograph on silica gel eluting sequentially with 10% ethyl acetate/hexane and 20% ethyl acetate/hexane to give the title compound as a solid.

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EXAMPLE 58

(S)-N-(2-Methoxybenzyl)-N-methyl-2-[N'-(t-butoxycarbonyl)-allylamino]-3-(naphth-2-yl)-propionamide

Scheme B, optional step 1:

Combine (S)-N-(2-methoxybenzyl)-N-methyl-2-[N'-(t-butoxycarbonyl)amino]-3-(naphth-2-yl)-propionamide (0.63 g, 1.41 mmol) and THF/DMF (15 mL/5 mL) and cool in an ice bath at 0°C. Add sodium hydride (0.067 g, 60% in oil, 2.82 mmol) and allyl bromide (0.73 mL, 8.46 mmol). Allow the reaction to warm to ambient temperature and then heat to reflux for 18 hours. Pour the reaction mixture into a saturated aqueous solution of ammonium chloride. Separate the layers and extract the aqueous layer with dichloromethane. Combine the organic layers. Dry over MgSO<sub>4</sub>, filter, and evaporate *in vacuo*. Chromatograph on silica gel eluting with 10% ethyl acetate/hexane to give the title compound: TLC R<sub>f</sub>=0.55 (silica gel, 20% ethyl acetate/hexane).



-59-

EXAMPLE 59

(S)-N-Benzyl-N-methyl-2-[N'-(t-butoxycarbonyl)-2-oxo-ethylamino]-3-phenyl-propionamide

5 Scheme B, step q:

- Combine (S)-N-benzyl-N-methyl-2-[N'-(t-butoxycarbonyl)-allylamino]-3-phenyl-propionamide (10.04 g, 24.5 mmol), and pyridine (0.13 ml) in dichloromethane/methanol (300mL/30 mL). Cool to -78° C. Pass ozonized oxygen through the solution until a persistent light blue color is obtained. Pass nitrogen through the solution until the blue color dissipates. Add dimethyl sulfide (55 mL). Allow the reaction mixture to warm to ambient temperature and stir for 16 hours. Concentrate *in vacuo* to obtain a residue.
- 15 Dilute the residue with ethyl acetate and extract with water. Separate the layers, dry the organic layer over MgSO<sub>4</sub>, filter, and evaporate *in vacuo*. Chromatograph on silica gel eluting with 10% ethyl acetate/hexane to give the title compound: TLC R<sub>f</sub>=0.53 (silica gel, 10% ethyl acetate/hexane).
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EXAMPLE 60

(S)-N-(2-Methoxybenzyl)-N-methyl-2-[N'-(t-butoxycarbonyl)-2-oxo-ethylamino]-3-phenyl-propionamide

25 Scheme D, step q:

- Combine (S)-N-(2-methoxybenzyl)-N-methyl-2-[N'-(t-butoxycarbonyl)-allylamino]-3-phenyl-propionamide (0.66 g, 1.52 mmol), N-methylmorpholine-N-oxide (0.20 g, 1.67 mmol), acetone (5 mL), and water (5 mL). Add osmium tetroxide (0.78 mL, 0.04M in THF, 0.032 mmol) and stir under an inert atmosphere for 18 hours. Pour the reaction mixture into a saturated solution of sodium bisulfite and extract the intermediate diol into ethyl acetate. Dry the separated organic layer over MgSO<sub>4</sub>, filter, and evaporate *in vacuo* to give the crude diol which is taken on to the next step without further purification. Dissolve the crude diol in chloroform (10 mL). Add a solution of lead tetraacetate
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-60-

(0.74 g, 1.67 mmol) in chloroform (10 mL). Stir for 30 minutes and then pour the reaction mixture into a saturated solution of sodium bicarbonate. Extract with dichloromethane and separate the organic layer. Dry the  
5 separated organic layer over  $\text{MgSO}_4$ , filter and evaporate *in vacuo* to give the title compound which may be used without further purification.

EXAMPLE 61

10 (S)-N-(3,4,5-Trimethoxybenzyl)-N-methyl-2-[N'-(t-butoxycarbonyl)-2-oxo-ethylamino]-3-phenyl-propionamide

Scheme B, step g:

Combine (S)-N-(3,4,5-trimethoxybenzyl)-N-methyl-2-[N'-(t-butoxycarbonyl)-2-allylamino]-3-phenyl-propionamide  
15 (0.50 g, 1.0 mmol), N-methylmorpholine-N-oxide (0.13 g, 1.1 mmol), acetone (15 mL), and water (20 mL). Add osmium tetroxide (0.51 mL, 0.04M in THF, 0.021 mmol) and stir under an inert atmosphere for 18 hours. Pour the reaction mixture into a saturated solution of sodium bisulfite and  
20 extract the intermediate diol into ethyl acetate. Dry the separated organic layer over  $\text{MgSO}_4$ , filter, and evaporate *in vacuo*. Take the crude diol on to the next step without further purification. Dissolve the crude diol in chloroform (10 mL). Add lead tetraacetate (0.48 g, 1.1  
25 mmol) as a solution in chloroform (10 mL). Stir for 30 minutes. Pour the reaction into a saturated aqueous solution of sodium bicarbonate and extract with dichloromethane. Dry the separated organic layer over  $\text{MgSO}_4$ , filter and evaporate *in vacuo* to give the title  
30 compound. The title compound may be used without further purification.

EXAMPLE 62

35 (S)-N-Benzyl-N-methyl-2-[N'-(t-butoxycarbonyl)-2-oxo-ethylamino]-3-(naphth-2-yl)-propionamide

Scheme B, step g:

-61-

Combine (S)-N-benzyl-N-methyl-2-[N'-(t-butoxycarbonyl)-allylamino]-3-(naphth-2-yl)-propionamide (3.34 g, 7.29 mmol), and pyridine (0.03 ml) in dichloromethane/methanol (66 mL/7 mL). Cool to -78° C. Pass ozonized oxygen through the solution until a persistent light blue color is obtained. Pass nitrogen through the solution until the blue color dissipates. Add dimethyl sulfide (12 mL). Allow the reaction mixture to warm to ambient temperature and stir for 16 hours. Concentrate *in vacuo* to obtain a residue. Dilute the residue with ethyl acetate and extract with water. Separate the layers, dry the organic layer over MgSO<sub>4</sub>, filter, and evaporate *in vacuo*. Chromatograph on silica gel eluting with 20% ethyl acetate/hexane to give the title compound: TLC R<sub>f</sub>=0.70 (silica gel, 50% ethyl acetate/hexane).

#### EXAMPLE 63

(S)-N-(3,4-Dichlorobenzyl)-N-methyl-2-[N'-(t-butoxycarbonyl)-2-oxo-ethylamino]-3-(naphth-2-yl)-propionamide

Scheme B, step g:

Combine (S)-N-(3,4-dichlorobenzyl)-N-methyl-2-[N'-(t-butoxycarbonyl)-allylamino]-3-(naphth-2-yl)-propionamide (0.26 g, 0.50 mmol), N-methylmorpholine-N-oxide (0.065 g, 0.55 mmol), acetone (10 mL), tetrahydrofuran (5 mL), and water (5 mL). Add osmium tetroxide (0.26 mL, 0.04M in THF, 0.042 mmol) and stir under an inert atmosphere for 18 hours. Pour the reaction mixture into a saturated solution of sodium bisulfite and extract the intermediate diol into ethyl acetate. Dry the separated organic layer over MgSO<sub>4</sub>, filter, and evaporate *in vacuo* to give the crude diol which is taken on to the next step without further purification. Dissolve the crude diol in chloroform (10 mL). Add a solution of lead tetraacetate (0.24 g, 0.55 mmol) in chloroform (10 mL). Stir for 30 minutes and then pour the reaction mixture into a saturated solution of sodium bicarbonate. Extract with dichloromethane and separate the

-62-

organic layer. Dry the separated organic layer over  $\text{MgSO}_4$ , filter and evaporate *in vacuo* to give the title compound which may be used without further purification.

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EXAMPLE 64

(S)-N-(2-Methoxybenzyl)-N-methyl-2-[N'-(t-butoxycarbonyl)-2-oxo-ethylamino]-3-(naphth-2-yl)-propionamide

Scheme B, step q:

Combine (S)-N-(2-methoxybenzyl)-N-methyl-2-[N'-(t-butoxycarbonyl)-allylamino]-3-(naphth-2-yl)-propionamide (0.46 g, 0.96 mmol), N-methylmorpholine-N-oxide (0.12 g, 1.06 mmol), acetone (20 mL), and water (10 mL). Add osmium tetroxide (0.50 mL, 0.04M in THF, 0.02 mmol) and stir under an inert atmosphere for 18 hours. Pour the reaction mixture into a saturated solution of sodium bisulfite and extract the intermediate diol into ethyl acetate. Dry the separated organic layer over  $\text{MgSO}_4$ , filter, and evaporate *in vacuo* to give the crude diol which is taken on to the next step without further purification. Dissolve the crude diol in chloroform (10 mL). Add a solution of lead tetraacetate (0.46 g, 1.06 mmol) in chloroform (10 mL). Stir for 30 minutes and then pour the reaction mixture into a saturated solution of sodium bicarbonate. Extract with dichloromethane and separate the organic layer. Dry the separated organic layer over  $\text{MgSO}_4$ , filter and evaporate *in vacuo* to give the title compound which may be used without further purification.

EXAMPLE 65

30 (S)-N-Benzyl-N-methyl-2-[N'-(t-butoxycarbonyl)-3-hydroxypropylamino]-3-phenyl-propionamide

Scheme B, optional step h:

Cool a solution of borane (1.5 mL, 1M in THF, 1.5 mmol) to 0°C in an ice-bath under an inert atmosphere. Add cyclohexene (0.31 mL, 3.1 mmol) and stir for 15 minutes with continued cooling. Add the suspension of dicyclohexylborane in THF prepared above to (S)-N-Benzyl-N-

-63-

meth-1-2-{N'-(t-butoxycarbonyl)-allylamino}-3-phenyl-  
propionamide (2 mmol) and stir in an ice-bath for 15  
minutes. Warm to ambient temperature and stir for 2 hours.  
Dilute the mixture with pH 7 phosphate buffer (40 mL) and  
5 ethanol (20 mL). Add 30% hydrogen peroxide (8 mL). Stir at  
ambient temperature for 20 hours. Concentrate *in vacuo* to  
obtain a residue. Dilute the reaction mixture with ethyl  
acetate and extract with water. Separate the layers, dry  
the organic layer over MgSO<sub>4</sub>, filter, and evaporate *in vacuo*.  
10 Chromatograph on silica gel to give the title compound.

EXAMPLE 66

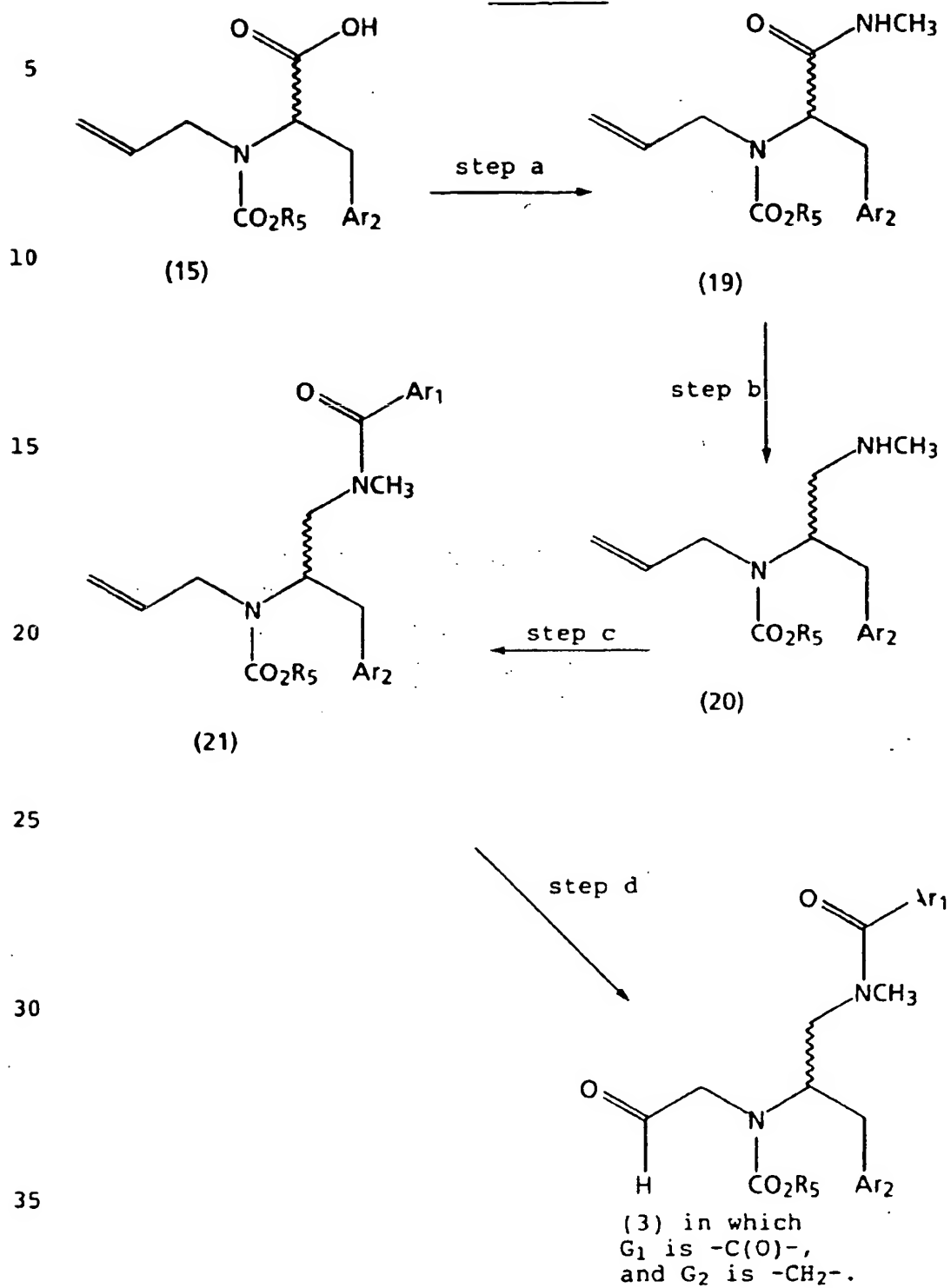
(S)-N-Benzyl-N-methyl-2-[N'-(t-butoxycarbonyl)-3-oxo-  
propylamino]-3-phenyl-propionamide

15 Scheme B, optional step i:

Combine (S)-N-Benzyl-N-methyl-2-[N'-(t-butoxycarbonyl)-  
3-hydroxypropylamino]-3-phenyl-propionamide (20 mmol),  
triethylamine (10 mmol), and dimethyl sulfoxide (4 mL).  
Add the solution prepared above to a solution of  
20 pyridine/sulfur trioxide complex (6.4 mmol) in dimethyl  
sulfoxide (12 mL). Stir for 1 hour. Dilute the reaction  
mixture with ethyl acetate and extract with water.  
Separate the layers, dry the organic layer over MgSO<sub>4</sub>,  
filter, and evaporate *in vacuo* to give the title compound  
25 which is taken to the next step without further  
purification.

A general synthetic procedure is set forth in Scheme C  
for preparing the aldehyde of structure (3), in which G<sub>1</sub> is  
30 -C(O)- and G<sub>2</sub> is -CH<sub>2</sub>-, used as a starting material in  
Scheme A.1. The reagents and starting materials are  
readily available to one of ordinary skill in the art. In  
Scheme C, all substituents, unless otherwise indicated, are  
as previously defined.

## Scheme C



In Scheme C, step a, an appropriate allyl-carbamate acid of structure (15) prepared using the methods of Scheme B undergoes an amidation reaction with methylamine or a salt of methylamine to give an allyl-carbamate acid-N-methyl amide of structure (19).

An appropriate allyl-carbamate acid of structure (15) is one in which the stereochemistry,  $R_5$ , and  $Ar_2$  are as desired in the product of formula (1) or is one which gives rise after resolution or deprotection to stereochemistry or  $Ar_2$  and  $R_3$  as desired in the final product of formula (1).

An amidation reaction may proceed through an activated intermediate, such as a mixed anhydride or a (O)-hydroxybenzotriazole, which may be prepared but is not necessarily isolated before the addition of methylamine or salt of methylamine.

For example, an appropriate allyl-carbamate acid of structure (15) is contacted with 1.2 to 1.7 equivalents of a suitable base, such as N-methylmorpholine, in a suitable solvent, such as tetrahydrofuran. Generally, the reaction mixture is cooled to a temperature of between  $-50^{\circ}\text{C}$  and  $0^{\circ}\text{C}$  with  $-25^{\circ}\text{C}$  to  $-20^{\circ}\text{C}$  being preferred, before the addition of 1.2 to 1.7 equivalents of isobutyl chloroformate. Generally, the reaction is allowed to stir for 30 minutes to 3 hours to allow for the formation of the mixed anhydride, an activated intermediate. While maintaining the temperature at between  $-50^{\circ}\text{C}$  and  $0^{\circ}\text{C}$  methylamine or a salt of methyl amine is added. The reaction may, after the addition of amine is complete, be warmed to room temperature. The reaction requires from 2 to 48 hours. The product can be isolated and purified by techniques well known in the art, such as extraction, evaporation, chromatography, and recrystallization.

Alternatively, for example, an appropriate allyl-carbamate acid of structure (15) is contacted with a slight molar excess of methylamine or a salt of methylamine and 1-hydroxybenzotriazole hydrate in the presence of a slight molar excess of a coupling agent, such as dicyclohexylcarbodiimide or 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide. The reaction is carried out in the presence of a suitable base, such as diisopropylethylamine. The reaction is carried out in a suitable solvent, such as dichloromethane or chloroform. The product can be isolated and purified by techniques well known in the art, such as extraction, evaporation, chromatography, and recrystallization.

15

In Scheme C, step b, an allyl-carbamate acid-N-methyl amide of structure (19) is reduced to give an N-methylamino compound of structure (20).

For example, an allyl-carbamate acid-N-methyl amide of structure (19) is contacted with a suitable reducing agent, such as diisobutylaluminum hydride or lithium aluminum hydride with diisobutylaluminum hydride being preferred. The reaction is carried out in a suitable solvent, such as tetrahydrofuran or toluene. Generally, the reaction is carried out at temperatures of from -20°C to the refluxing temperature of the solvent. After an appropriate work-up, as is well known in the art, the work-up used depends on the products produced and the reducing reagent used, the product can be isolated and purified by techniques well known in the art, such as extraction, evaporation, chromatography, and recrystallization.

In Scheme C, step c, a N-methylamino compound of structure (20) is aroylated with an appropriate aroyl acid chloride to give a N-methyl aroylamide of structure (21).



An appropriate aroyl acid chloride,  $\text{Ar}_1\text{C}(\text{O})\text{Cl}$ , is one in which  $\text{Ar}_1$  is as desired in the product of formula (1) or give rise after deprotection to  $\text{Ar}_1$  desired in the final product of formula (1).

For example, a N-methylamino compound of structure (20) is contacted with an appropriate aroyl acid chloride,  $\text{Ar}_1\text{C}(\text{O})\text{Cl}$ . The reaction is carried out in the presence of a suitable base, such as triethylamine, diisopropylethylamine, or pyridine. The reaction is carried out in a suitable solvent, such as dichloromethane, chloroform, pyridine, dioxane, tetrahydrofuran, or water. Generally, the reaction is carried out at temperatures of from  $-20^\circ\text{C}$  to the refluxing temperature of the solvent. The product can be isolated and purified by techniques well known in the art, such as extraction, evaporation, chromatography, and recrystallization.

In Scheme C, step d, a N-methyl aroylamide of structure (21) is converted to an aldehyde of structure (3) in which  $\text{G}_1$  is  $-\text{C}(\text{O})-$  and  $\text{G}_2$  is  $-\text{CH}_2-$ . A N-methyl aroyl amide of structure (21) may be converted to an aldehyde of structure (3) in which  $\text{G}_1$  is  $-\text{C}(\text{O})-$  and  $\text{G}_2$  is  $-\text{CH}_2-$  by either; ozonolysis in the presence of methanol followed by a reductive work-up, or an osmium tetroxide mediated formation of an intermediate diol followed by oxidative cleavage with lead tetraacetate or sodium meta-periodate.

For example, a N-methyl aroylamide of structure (21) is contacted with ozone in the presence of methanol. The reaction is carried out in a suitable solvent, such as dichloromethane. Generally, the reaction is carried out at temperature of from  $-100^\circ\text{C}$  to  $-60^\circ\text{C}$ , with  $-70^\circ\text{C}$  being preferred. The reaction is worked-up reductively by the addition of a suitable reducing agent, such as tributylphosphine or dimethyl sulfide. The product may be

isolated from the reaction zone by evaporation and may be used without further purification. The product may be purified by techniques well known in the art, such as chromatography and recrystallization.

Alternatively, for example, a N-methyl aroylamide of structure (21) is contacted with osmium tetroxide to give an intermediate diol. The reaction may be carried out using a 0.01 to 0.05 molar equivalents of osmium tetroxide and a slight molar excess of an oxidant, such as N-methylmorpholine-N-oxide. The reaction is carried out in a solvent, such as acetone/water mixtures. The reaction is carried out at ambient temperature and requires from 12 to 48 hours. The reaction mixture is added to a saturated solution of sodium bisulfite and the intermediate diol is isolated by extraction and evaporation and used without further purifications. The intermediate diol is contacted with a slight molar excess of lead tetraacetate or sodium meta-periodate. Generally, the reaction is carried out in a solvent, such as chloroform. The reaction is carried out at ambient temperature and requires from 30 minutes to 8 hours. The product may be isolated from the reaction zone by extraction and evaporation and may be used without further purification. The product may be purified by techniques well known in the art, such as chromatography and recrystallization.

#### EXAMPLE 67

(S)-N-Methyl-2-[N'-(t-butoxycarbonyl)-allylamino]-3-phenyl-propionamide

##### Scheme C, step a:

Combine (S)-2-[N-(t-butoxycarbonyl)-allylamino]-3-phenyl-propionic acid (0.7 g, 2.29 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.50 g, 2.52 mmol), 1-hydroxybenzotriazole (0.38 g, 2.52 mmol), methylamine hydrochloride (0.17 g, 2.52 mmol) and diisopropylethylamine (0.59 mL, 2.52 mmol) in

dichloromethane (23 mL) and stir for 18 hours. Dilute with ethyl acetate and extract with 1M hydrochloric acid, a saturated aqueous solution of sodium bicarbonate and a saturated aqueous solution of sodium chloride. Dry the separated organic layer over  $\text{MgSO}_4$ , filter and evaporate *in vacuo*. Chromatograph on silica gel eluting sequentially with 5% methanol/dichloromethane and 10% methanol/dichloromethane to give the title compound: TLC  $R_f=0.44$  (silica gel, 30% ethyl acetate/hexane).

#### EXAMPLE 68

##### (S)-N-Methyl-2-[N'-(t-butoxycarbonyl)-allylamino]-3-phenyl-propylamine

##### 15 Scheme C, step b:

Dissolve (S)-N-methyl-2-[N'-(t-butoxycarbonyl)-allylamino]-3-phenyl-propionamide (0.31 g, 0.98 mmol) in dichloromethane (10 mL) and cool in a dry ice/acetone bath to  $-78^\circ\text{C}$ . Add diisobutylaluminum hydride (1.96 mL, 1.5M in toluene, 2.94 mmol). Allow to warm slowly to ambient temperature and stir for 16 hours. Slowly add a 15% aqueous solution of sodium hydroxide (3.0 mL). Extract with dichloromethane, dry the organic layer over  $\text{MgSO}_4$ , filter, and evaporate *in vacuo* to give the title compound as a mixture which is taken on to the next step without further purification.

#### EXAMPLE 69

##### (S)-N-Methyl-N-[[2-[N'-(t-butoxycarbonyl)-allylamino]-3-phenylpropyl]-benzamide

##### 30 Scheme C, step c:

Combine (S)-N-methyl-2-[N'-(t-butoxycarbonyl)-allylamino]-3-phenyl-propylamine (1.23 g, 4.25 mmol) and diisopropylethylamine (0.36 mL, 2.0 mmol) in dichloromethane (20 mL). Cool to  $0^\circ\text{C}$  in an ice bath. Add benzoyl chloride (0.24 mL, 2.0 mmol) and stir the reaction at  $0^\circ\text{C}$  for 2 hours. Extract the reaction mixture with water, dry the organic layer over  $\text{MgSO}_4$ , filter, and

evaporate *in vacuo*. Chromatograph on silica gel eluting with 20% ethyl acetate/hexane to give the title compound: TLC  $R_f=0.59$  (silica gel, 20% ethyl acetate/hexane).

5

EXAMPLE 70

(S)-N-Methyl-N-[[2-[N'-(t-butoxycarbonyl)-allylamino]-3-phenylpropyl]-(3,4,5-trimethoxy)benzamide

Scheme C, step c:

- 10        Combine (S)-N-Methyl-2-[N'-(t-butoxycarbonyl)-allylamino]-3-phenyl-propylamine (0.57 g, 1.87 mmol) and diisopropylethylamine (0.65 mL, 3.74 mmol) in dichloromethane (40 mL). Cool to 0°C in an ice bath. Add 3,4,5-trimethoxybenzoyl chloride (0.43 g, 1.87 mmol) and
- 15        stir the reaction at 0°C for 4 hours. Extract the reaction mixture with water, dry the organic layer over  $MgSO_4$ , filter, and evaporate *in vacuo*. Chromatograph on silica gel eluting sequentially with 5% ethyl acetate/hexane, 20% ethyl acetate/hexane, 35% ethyl acetate/hexane to give the
- 20        title compound.

EXAMPLE 71

(S)-N-Methyl-N-[[2-[N'-(t-butoxycarbonyl)-2-oxo-ethylamino]-3-phenylpropyl]-(3,4,5-trimethoxy)benzamide

- 25        Scheme C, optional step d:

- Combine (S)-N-methyl-N-[[2-[N'-(t-butoxycarbonyl)-allylamino]-3-phenylpropyl]-(3,4,5-trimethoxy)benzamide (0.145 g, 0.29 mmol), N-methylmorpholine-N-oxide (0.037 g, 0.32 mmol), acetone (5 mL), and water (5 mL). Add osmium
- 30        tetroxide (0.15 mL, 0.04M in THF, 0.006 mmol) and stir under an inert atmosphere for 18 hours. Pour the reaction mixture into a saturated solution of sodium bisulfite and extract the intermediate diol into ethyl acetate. Dry the separated organic layer over  $MgSO_4$ , filter, and evaporate *in*
- 35        *vacuo* to obtain the crude diol which is taken on to the next step without further purification. Dissolve the crude diol in chloroform (10 mL). Add lead tetraacetate (0.32 g, 0.32 mmol) as a solution in chloroform (10 mL). Stir for 30

minutes. Pour the reaction into a saturated aqueous solution of sodium bicarbonate and extract with dichloromethane. Dry the separated organic layer over 5 MgSO<sub>4</sub>, filter and evaporate *in vacuo* to give the title compound: TLC R<sub>f</sub>=0.79 (silica gel, 10% methanol/dichloromethane). The title compound may be used without further purification.

10

EXAMPLE 72

(S)-N-Methyl-N-[(2-[N'-(t-butoxycarbonyl)-2-oxo-ethylamino]-3-phenylpropyl)-benzamide

Scheme C, optional step d:

Combine (S)-N-methyl-N-[(2-[N'-(t-butoxycarbonyl)-allylamino]-3-phenylpropyl)-benzamide (0.14 g, 0.35 mmol), 15 N-methylmorpholine-N-oxide (0.044 g, 0.38 mmol), acetone (5 mL), and water (5 mL). Add osmium tetroxide (0.18 mL, 0.04M in THF, 0.0074 mmol) and stir under an inert atmosphere for 18 hours. Pour the reaction mixture into a saturated solution of sodium bisulfite and extract the 20 intermediate diol into ethyl acetate. Dry the separated organic layer over MgSO<sub>4</sub>, filter, and evaporate *in vacuo* to obtain the crude diol which is taken on to the next step without further purification. Dissolve the crude diol in 25 chloroform (5 mL). Add lead tetraacetate (0.16 g, 0.38 mmol) as a solution in chloroform (5 mL). Stir for 30 minutes. Pour the reaction into a saturated aqueous solution of sodium bicarbonate and extract with dichloromethane. Dry the separated organic layer over 30 MgSO<sub>4</sub>, filter and evaporate *in vacuo* to give the title compound: TLC R<sub>f</sub>=0.76 (silica gel, 50% ethyl acetate/hexane). The title compound may be used without further purification.

35

A general synthetic procedure is set forth in Scheme D for preparing the aldehyde of structure (3) in which G<sub>1</sub> is -CH<sub>2</sub>- and G<sub>2</sub> is -CH<sub>2</sub>- used as a starting material in Scheme A.1. The reagents and starting materials are readily

available to one of ordinary skill in the art. In Scheme D, all substituents, unless otherwise indicated, are as previously defined.

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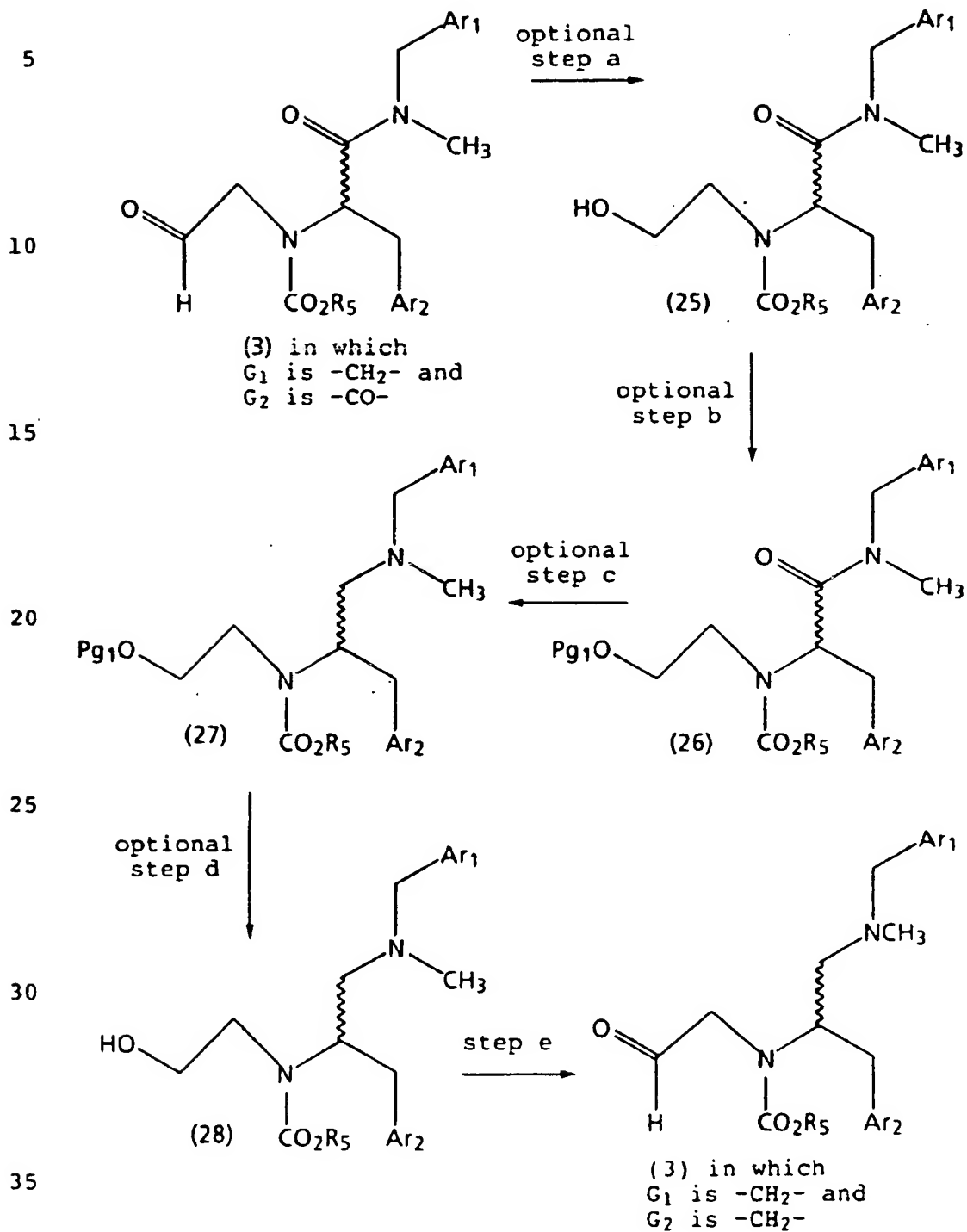
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## Scheme D



-74-

In Scheme D, optional step a, an appropriate aldehyde of structure (3) is reduced using a suitable reducing agent to give an alcohol amide of structure (25).

5       An appropriate aldehyde of structure (3) is one in which  $G_1$  is  $-CH_2-$ ,  $G_2$  is  $-C(O)-$ , stereochemistry,  $R_5$ ,  $Ar_1$ ,  $Ar_2$  are as is desired in the product of formula (1) or can also be one in which the stereochemistry and groups  $Ar_1$  and  $Ar_2$ , and  $R_5$  give rise after resolution and deprotection or  
10       modification to stereochemistry and groups  $Ar_1$ ,  $Ar_2$ , and  $R_3$  as desired in the final product of formula (1). For the preparation of aldehydes of structure (3) in which  $G_1$  is  $-CH_2-$  and  $G_2$  is  $-CH_2-$  the use of aldehydes (3) in which  $G_1$  is  $-CH_2-$ ,  $G_2$  is  $-C(O)-$ , and  $R_5$  is t-butyl are preferred.

15

For example, an appropriate aldehyde of structure (3) is contacted with from 1 to 4 equivalents of a suitable reducing agent, such as sodium borohydride. A suitable reducing agent in optional step a reduces an aldehyde and  
20       does not affect an amide of any protecting group which may be present. The reaction is carried out in a suitable solvent, such as methanol or ethanol. Generally, the reaction is carried out at temperatures of from  $0^\circ C$  to the refluxing temperature of the solvent. Generally, the  
25       reactions require from 1 to 72 hours. The product can be isolated and purified by techniques well known in the art, such as quenching, extraction, evaporation, chromatography, and recrystallization.

30       In Scheme D, optional step b, an alcohol amide of structure (25) is protected using a suitable hydroxy protecting group,  $Pg_1$ , to give a protected hydroxy amide compound of structure (26). An alcohol amide of structure (25) may be prepared as taught in Scheme D, optional step  
35       a.



-75-

A suitable hydroxy protecting group is one which allows for the reduction of an amide, such protecting groups include but are not limited to tetrahydropyran-2-yl, t-butyldimethylsilyl, or t-butyldiphenylsilyl. The selection and use of suitable hydroxy protecting groups is well known and appreciated in the art and is described in Protecting Groups in Organic Synthesis by T. Greene, Wiley-Interscience (1981).

10 In Scheme D, optional step c, a protected hydroxy amide compound of structure (26) is reduced using a suitable amide reducing agent to give a protected hydroxy amine compound of structure (27).

15 For example, a protected hydroxy amide compound of structure (26) is contacted with from 1 to 5 equivalents of a suitable amide reducing agent, such as lithium aluminum hydride, diisobutylaluminum hydride, or borane dimethyl sulfide complex. The reaction is carried out in a suitable  
20 solvent, such as tetrahydrofuran, toluene, or diethyl ether. Generally, the reaction is carried out at temperatures of from 0°C to the refluxing temperature of the solvent. Generally, the reactions require from 1 to 72 hours. The product can be isolated and purified by  
25 techniques well known in the art, such as quenching, extraction, evaporation, chromatography, and recrystallization.

In Scheme D, optional step d, a protected hydroxy amine  
30 compound of structure (27) is deprotected to give a hydroxy amine compound of structure (28).

The use and removal of suitable hydroxy protecting groups is well known and appreciated in the art and is  
35 described in Protecting Groups in Organic Synthesis by T. Greene, Wiley-Interscience (1981).

-76-

As is appreciated by one of ordinary skill in the art, either an aldehyde of structure (3) in which G<sub>1</sub> is -CH<sub>2</sub>- and G<sub>2</sub> is -C(O)- or an alcohol of structure (25) might be directly reduced to a hydroxy amine compound of structure (28) using a suitable amide reducing agent, such as lithium aluminum hydride, diisobutyl aluminum hydride, or borane dimethyl sulfide complex as taught in Scheme D, optional step d.

10 In Scheme D, step e, a hydroxy amine compound of structure (28) is oxidized to give an aldehyde of structure (3) in which G<sub>1</sub> is -CH<sub>2</sub>-, G<sub>2</sub> is -CH<sub>2</sub>-.

Oxidations of alcohols in compounds containing tertiary amines is well known and appreciated in the art and are described in T. P. Burkholder and P. L. Fuchs, *J. Am. Chem. Soc.* 112, 9601 (1990) and M. P. Kotick et al. *J. Med. Chem.* 26, 1050 (1983).

20 For example, two molar equivalents of dimethyl sulfoxide are added dropwise to a solution of trifluoroacetic anhydride in dichloromethane, at approximately -60°C. After the addition is complete, the reaction is stirred for approximately two minutes. A molar equivalent of a hydroxy amine compound of structure (28) as a solution in dichloromethane is added dropwise. After the addition is complete the reaction mixture is stirred for approximately forty minutes, then a 3-fold to 5-fold excess of triethylamine is added. The reaction mixture is 25 allowed to stir with warming to ambient temperature over 1 hour to 5 hours. The product can be isolated and purified by techniques well known in the art, such as extraction, evaporation, chromatography, and recrystallization.

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EXAMPLE 75

(S)-N-Benzyl-N-methyl-2-[N-(t-butoxycarbonyl)-2-hydroxy-ethylamino]-3-phenyl-propionamide

-77-

Scheme D, optional step a:

Combine (S)-N-benzyl-N-methyl-2-[N-(t-butoxycarbonyl)-2-oxo-ethylamino]-3-phenyl-propionamide (5.0 mmol) and sodium borohydride (5.0 mmol) in ethanol (20 mL). Stir for 16 hours. Concentrate *in vacuo* to obtain a residue. Dilute the residue with ethyl acetate and extract with 0.5 M hydrochloric acid solution and water. Separate the layers, dry the organic layer over MgSO<sub>4</sub>, filter, and evaporate *in vacuo* to give the title compound.

10

EXAMPLE 76

(S)-N-Benzyl-N-methyl-2-[N-(t-butoxycarbonyl)-2-tetrahydropyran-2-yl-oxy-ethylamino]-3-phenyl-propionamide

Scheme D, optional step b:

Combine (S)-N-benzyl-N-methyl-2-[N-(t-butoxycarbonyl)-2-hydroxy-ethylamino]-3-phenyl-propionamide (4 mmol) p-toluenesulfonic acid (50 mg), and dihydropyran (4 mmol) in anhydrous dichloromethane. After 8 hours, partition the reaction mixture between dichloromethane and 0.5 M sodium hydroxide solution. Separate the organic layer and dry over MgSO<sub>4</sub>, filter, and evaporate *in vacuo* to give the title compound.

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EXAMPLE 77

(S)-N-Benzyl-N-methyl-2-[N-(t-butoxycarbonyl)-2-tetrahydropyran-2-yl-oxy-propylamino]-3-phenyl-propionamide

Scheme D, optional step b:

Combine (S)-N-Benzyl-N-methyl-2-[N'-(t-butoxycarbonyl)-3-hydroxypropylamino]-3-phenyl-propionamide (4 mmol) p-toluenesulfonic acid (50 mg), and dihydropyran (4 mmol) in anhydrous dichloromethane. After 8 hours, partition the reaction mixture between dichloromethane and 0.5 M sodium hydroxide solution. Separate the organic layer and dry over MgSO<sub>4</sub>, filter, and evaporate *in vacuo* to give the title compound.

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EXAMPLE 78

-78-

(S)-N-Benzyl-N-methyl-N-[N-(t-butoxycarbonyl)-2-tetrahydropyran-2-yl-oxy-ethylamino]-3-phenyl-propylamine  
Scheme D, optional step c:

- Combine (S)-N-benzyl-N-methyl-2-[N-(t-butoxycarbonyl)-2-tetrahydropyran-2-yl-oxy-ethylamino]-3-phenyl-propionamide (4 mmol) and lithium aluminum hydride (8 mmol) in tetrahydrofuran (20 mmol). Heat to reflux for 48 hours. Cool to ambient temperature, slowly add water (0.3 mL), 15% sodium hydroxide solution (0.3 mL), and water (0.9 mL). Stir until all the reagent is quenched. Filter and evaporate *in vacuo* to obtain a residue. Partition the residue between ethyl acetate and water. Separate the organic layer and dry over MgSO<sub>4</sub>, filter, and evaporate *in vacuo* to give the title compound.

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EXAMPLE 79

(S)-N-Benzyl-N-methyl-N-[N-(t-butoxycarbonyl)-2-tetrahydropyran-2-yl-oxy-propylamino]-3-phenyl-propylamine  
Scheme D, optional step c:

- Combine (S)-N-benzyl-N-methyl-2-[N-(t-butoxycarbonyl)-2-tetrahydropyran-2-yl-oxy-propylamino]-3-phenyl-propionamide (4 mmol) and lithium aluminum hydride (8 mmol) in tetrahydrofuran (20 mmol). Heat to reflux for 48 hours. Cool to ambient temperature, slowly add water (0.3 mL), 15% sodium hydroxide solution (0.3 mL), and water (0.9 mL). Stir until all the reagent is quenched. Filter and evaporate *in vacuo* to obtain a residue. Partition the residue between ethyl acetate and water. Separate the organic layer and dry over MgSO<sub>4</sub>, filter, and evaporate *in vacuo* to give the title compound.

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EXAMPLE 80

(S)-N-Benzyl-N-methyl-N-[N-(t-butoxycarbonyl)-2-hydroxy-ethylamino]-3-phenyl-propylamine

- 35 Scheme D, optional step d:

Combine (S)-N-benzyl-N-methyl-N-[N-(t-butoxycarbonyl)-2-tetrahydropyran-2-yl-oxy-ethylamino]-3-phenyl-propylamine

-79-

(2.0 mmol) and p-toluenesulfonic acid (3 mmol) in methanol (20 mL). After 8 hours, vaporate *in vacuo*. Partition the residue between dichloromethane and 0.5 M sodium hydroxide solution. Separate the organic layer and dry over MgSO<sub>4</sub>, filter, and evaporate *in vacuo* to give the title compound.

#### EXAMPLE 81

(S)-N-Benzyl-N-methyl-N-[N-(t-butoxycarbonyl)-2-hydroxy-propylamino]-3-phenyl-propylamine

10 Scheme D, optional step d:

Combine (S)-N-benzyl-N-methyl-N-[N-(t-butoxycarbonyl)-2-tetrahydropyran-2-yl-oxy-propylamino]-3-phenyl-propylamine (2.0 mmol) and p-toluenesulfonic acid (3 mmol) in methanol (20 mL). After 8 hours, evaporate *in vacuo*.  
15 Partition the residue between dichloromethane and 0.5 M sodium hydroxide solution. Separate the organic layer and dry over MgSO<sub>4</sub>, filter, and evaporate *in vacuo* to give the title compound.

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#### EXAMPLE 82

(S)-N-Methyl-N-benzyl-N-[2-[N'-(t-butoxycarbonyl)-2-oxo-ethylamino]-3-phenyl-propylamine

Scheme D, step e:

Combine trifluoroacetic acid anhydride (4.8 mmol) with  
25 dichloromethane (10 mL) and cool to -60°C. Add dropwise a solution of dimethyl sulfoxide (9.6 mmol) in dichloromethane (1 mL) while maintaining the temperature below -55°C. After addition is complete, stir for 2 minutes. Add a solution of (S)-N-benzyl-N-methyl-N-[N-(t-butoxycarbonyl)-2-hydroxy-ethylamino]-3-phenyl-propylamine  
30 (2 mmol) in dichloromethane and stir for 45 minutes. Cool the reaction to -78°C and add triethylamine (10 mmol) dropwise. Allow the reaction to warm to ambient temperature and stir for 45 minutes. Pour the reaction  
35 into water. Extract this mixture with diethyl ether. Separate the organic layer and dry over MgSO<sub>4</sub>, filter, and evaporate *in vacuo* to give the title compound.

-80-

EXAMPLE 83(S)-N-Methyl-N-benzyl-N-[2-[N'-(t-butoxycarbonyl)-2-oxo-propylamino]-3-phenyl-propylamine

- 5        Combine trifluoroacetic acid anhydride (4.8 mmol) with dichloromethane (10 mL) and cool to -60°C. Add dropwise a solution of dimethyl sulfoxide (9.6 mmol) in dichloromethane (1 mL) while maintaining the temperature below -55°C. After addition is complete, stir for 2
- 10       minutes. Add a solution of (S)-N-benzyl-N-methyl-N-(N-(t-butoxycarbonyl)-2-hydroxy-propylamino)-3-phenyl-propylamine (2 mmol) in dichloromethane and stir for 45 minutes. Cool the reaction to -78°C and add triethylamine (10 mmol) dropwise. Allow the reaction to warm to ambient
- 15       temperature and stir for 45 minutes. Pour the reaction into water. Extract this mixture with diethyl ether. Separate the organic layer and dry over MgSO<sub>4</sub>, filter, and evaporate *in vacuo* to give the title compound.

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-81-

The tachykinins are a class of neuropeptides which share a common C-terminus sequence, Phe-Xaa-Gly-Leu-Met-NH<sub>2</sub>. The tachykinins are widely distributed in the peripheral and central nervous systems where they bind to at least  
5 three receptors types. The NK<sub>1</sub>, NK<sub>2</sub>, and NK<sub>3</sub> receptors are defined by the preferred binding affinity of substance P, neurokinin A (NKA), and neurokinin B (NKB), respectively.

Antagonism of the effects of substance P on its  
10 preferred receptor, i.e. NK<sub>1</sub>, will not prevent the effects of NKA on its preferred receptor, i.e. NK<sub>2</sub>. Therefore, the potential benefits of an antagonist with affinity at both the NK<sub>1</sub> and NK<sub>2</sub> receptors would be to reduce or prevent clinical manifestations of diseases and conditions which  
15 are mediated through both receptors.

The use of tachykinin antagonists is indicated as therapy for a variety of tachykinin-mediated diseases and conditions including: cystitis; bronchoconstriction;  
20 hypersensitivity reactions; the treatment of pain; peripheral neuropathy; post-herpetic neuralgia; adverse immunological reactions; respiratory diseases, such as asthma, bronchitis, cough, rhinitis, and allergies and the like; ophthalmic diseases, such as conjunctivitis and  
25 vernal conjunctivitis; cutaneous diseases, such as contact dermatitis, atopic dermatitis, and urticaria; inflammatory diseases, such as rheumatoid arthritis and osteoarthritis, and the like; gastrointestinal conditions, such as Crohn's disease, emesis, and ulcerative colitis; conditions due to  
30 vasodilation, such as angina and migraine; and central nervous system diseases and conditions, such as anxiety, depression, psychosis, schizophrenia, dementia.

It is understood that tachykinin-mediated diseases and  
35 conditions are those diseases and conditions in which the tachykinins are involved, either in whole or in part, in their clinical manifestation(s). Moreover, the tachykinins

-82-

involvement is not necessarily causative of a particular tachykinin-mediated disease and condition. Tachykinin antagonists are useful in controlling or providing therapeutic relief of those tachykinin-mediated diseases  
5 and conditions.

The present invention provides new and useful tachykinin antagonists of formula (1) or stereoisomers or pharmaceutically acceptable salts thereof. More  
10 particularly, the present invention provides compounds of formula (1) which are NK<sub>1</sub> receptor antagonists, NK<sub>2</sub> receptor antagonists, and both NK<sub>1</sub> and NK<sub>2</sub> receptor antagonists.

In a further embodiment, the present invention provides  
15 a method of treating tachykinin-mediated diseases and conditions in a patient in need thereof comprising administering to said patient a therapeutically effective amount of a compound of formula (1). Various diseases and conditions described to be treated herein, are well known  
20 and appreciated by those skilled in the art. It is also recognized that one skilled in the art may affect the associated diseases and conditions by treating a patient presently afflicted with the diseases or conditions or by prophylactically treating a patient afflicted with the  
25 diseases or conditions with a therapeutically effective amount of the compounds of formula (1).

As used herein, the term "patient" refers to a warm blooded animal such as a mammal which is afflicted with a  
30 particular tachykinin-mediated disease or condition. It is understood that guinea pigs, dogs, cats, rats, mice, horses, cattle, sheep, and humans are examples of animals within the scope of the meaning of the term.

35 As used herein, the term "therapeutically effective amount" of a compound of formula (1) refers to an amount which is effective in controlling tachykinin-mediated



-83-

diseases and conditions. The term "controlling" is intended to refer to all processes wherein there may be a slowing, interrupting, arresting, or stopping of the progression of the diseases and conditions described herein, but does not necessarily indicate a total elimination of all disease and condition symptoms, and is intended to include prophylactic treatment of the tachykinin-mediated diseases and conditions.

10 A therapeutically effective amount can be readily determined by the attending diagnostician, as one skilled in the art, by the use of conventional techniques and by observing results obtained under analogous circumstances. In determining the therapeutically effective amount, the  
15 dose, a number of factors are considered by the attending diagnostician, including, but not limited to: the species of mammal; its size, age, and general health; the specific disease involved; the degree of or involvement in or the severity of the disease; the response of the individual  
20 patient; the particular compound administered; the mode of administration; the bioavailability characteristic of the preparation administered; the dose regimen selected; the use of concomitant medication; and other relevant circumstances.

25

A therapeutically effective amount of a compound of formula (1) is expected to vary from about 0.1 milligram per kilogram of body weight per day (mg/kg/day) to about 100 mg/kg/day. Preferred amounts are able to be  
30 determined by one skilled in the art.

In effecting treatment of a patient afflicted with tachykinin-mediated diseases and conditions described above, a compound of formula (1) can be administered in  
35 any form or mode which makes the compound bioavailable in an effective amount, including oral, inhalation, and parenteral routes. For example, compounds of formula (1)

-84-

can be administered orally, by inhalation of an aerosol or dry powder, subcutaneously, intramuscularly, intravenously, transdermally, intranasally, rectally, topically, and the like. Oral or inhalation

5 administration is generally preferred for treatment of respiratory diseases and conditions, e.g. asthma. One skilled in the art of preparing formulations can readily select the proper form and mode of administration depending upon the particular characteristics of the  
10 compound selected, the disease or condition to be treated, the stage of the disease or condition, and other relevant circumstances. (Remington's Pharmaceutical Sciences, 18th Edition, Mack Publishing Co. (1990)).

15 The compounds of the present invention can be administered alone or in the form of a pharmaceutical composition in combination with pharmaceutically acceptable carriers or excipients; the proportion and  
20 nature of which are determined by the solubility and chemical properties of the compound selected, the chosen route of administration, and standard pharmaceutical practice. The compounds of the present invention, while effective themselves, may be formulated and administered in the form of their pharmaceutically acceptable salts,  
25 such as acid addition salts or base addition salts, for purposes of stability, convenience of crystallization, increased solubility and the like.

In another embodiment, the present invention provides  
30 pharmaceutical compositions comprising a therapeutically effective amount of a compound of formula (1) in admixture or otherwise in association with one or more pharmaceutically acceptable carriers or excipients.

35 The pharmaceutical compositions are prepared in a manner well known in the pharmaceutical art. The carrier or excipient may be a solid, semi-solid, or liquid

-85-

material which can serve as a vehicle or medium for the active ingredient. Suitable carriers or excipients are well known in the art. The pharmaceutical composition may be adapted for oral, inhalation, parenteral, or topical  
5 use and may be administered to the patient in the form of tablets, capsules, aerosols, inhalants, suppositories, solution, suspensions, or the like.

The compounds of the present invention may be  
10 administered orally, for example, with an inert diluent or with an edible carrier. They may be enclosed in gelatin capsules or compressed into tablets. For the purpose of oral therapeutic administration, the compounds may be incorporated with excipients and used in the form of  
15 tablets, troches, capsules, elixirs, suspensions, syrups, wafers, chewing gums and the like. These preparations should contain at least 4% of the compound of the present invention, the active ingredient, but may be varied depending upon the particular form and may conveniently be  
20 between 4% to about 70% of the weight of the unit. The amount of the compound present in compositions is such that a suitable dosage will be obtained. Preferred compositions and preparations according to the present invention may be determined by someone skilled in the art.

25 The tablets, pills, capsules, troches and the like may also contain one or more of the following adjuvants: binders such as microcrystalline cellulose; gum tragacanth or gelatin; excipients such as starch or lactose, disintegrating agents such as alginic acid, Primogel, corn starch  
30 and the like; lubricants such as magnesium stearate or Sterotex; glidants such as colloidal silicon dioxide; and sweetening agents such as sucrose or saccharin may be added or a flavoring agent such as peppermint, methyl  
35 salicylate or orange flavoring. When the dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier such as polyethylene glycol or a fatty oil. Other dosage unit forms may

-86-

contain other various materials which modify the physical form of the dosage unit, for example, as coatings. Thus, tablets or pills may be coated with sugar, shellac, or other enteric coating agents. A syrup may contain, in addition to the present compounds, sucrose as a sweetening agent and certain preservatives, dyes and colorings and flavors. Materials used in preparing these various compositions should be pharmaceutically pure and non-toxic in the amounts used.

10

For the purpose of parenteral therapeutic administration, the compounds of the present invention may be incorporated into a solution or suspension. These preparations should contain at least 0.1% of a compound of the invention, but may be varied to be between 0.1 and about 50% of the weight thereof. The amount of the compound of formula (1) present in such compositions is such that a suitable dosage will be obtained. Preferred compositions and preparations are able to be determined by one skilled in the art.

15

The compounds of the present invention may also be administered by inhalation, such as by aerosol or dry powder. Delivery may be by a liquefied or compressed gas or by a suitable pump system which dispenses the compounds of the present invention or a formulation thereof. Formulations for administration by inhalation of compounds of formula (1) may be delivered in single phase, bi-phasic, or tri-phasic systems. A variety of systems are available for the administration by aerosol of the compounds of formula (1). Dry powder formulations are prepared by either pelletizing or milling the compound of formula (1) to a suitable particle size or by admixing the pelletized or milled compound of formula (1) with a suitable carrier material, such as lactose and the like. Delivery by inhalation includes the necessary container, activators, valves, subcontainers, and the like.

25

30

35

-87-

Preferred aerosol and dry powder formulations for administration by inhalation can be determined by one skilled in the art.

5       The compounds of the present invention may also be administered topically, and when done so the carrier may suitably comprise a solution, ointment or gel base. The base, for example, may comprise one or more of the following: petrolatum, lanolin, polyethylene glycols, bee  
10 wax, mineral oil, and the like; diluents such as water and alcohols; emulsifiers; and stabilizers. Topical formulations may contain a concentration of the formula (1) or its pharmaceutical salt from about 0.1 to about 10% w/v (weight per unit volume).

15

The solutions or suspensions may also include one or more of the following adjuvants: sterile diluents such as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other  
20 synthetic solvents; antibacterial agents such as benzyl alcohol or methyl paraben; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylene diaminetetraacetic acid; buffers such as acetates, citrates or phosphates and agents for the  
25 adjustment of tonicity such as sodium chloride or dextrose. The parenteral preparation can be enclosed in ampules, disposable syringes or multiple dose vials made of glass or plastic.

30       One skilled in the art can determine the NK<sub>1</sub> receptor and NK<sub>2</sub> receptor affinity *in vitro* as follows. The NK<sub>1</sub> receptor affinity of tachykinin antagonists is evaluated in guinea pig lungs (Keystone Biologicals, Cleveland, OH) and affinity for the NK<sub>2</sub> receptor is evaluated in HSKR-1  
35 cells (which are mouse 3T3 fibroblasts expressing the human jejunal NK<sub>2</sub> receptor). Tissues or cells are homogenized with a Polytron in 15 volumes of 50 mM Tris-

-88-

HCl buffer (pH 7.4, 4°C) and centrifuged. The pellet is resuspended in Tris-HCl buffer and is centrifuged; the pellet is washed twice by resuspension. The final pellet is resuspended at a concentration of 40 mg/ml for tissues and 20 mg/ml for cells in incubation buffer and remains at room temperature for at least 15 min prior to use.

Receptor binding is initiated by addition of 250 ul membrane preparation in duplicate to 0.1 nM of the following radioligands: <sup>125</sup>I-Bolton Hunter Lys-3 labeled substance P and <sup>125</sup>iodohistidyl-1-neurokinin A; in a final volume of 500 ul of buffer containing 50 mM Tris-HCl (pH 7.4 at room temperature), 0.1% bovine serum albumin, 2 mM MnCl<sub>2</sub>, 40 ug/ml bacitracin, 4 ug/ml leupeptin and chymostatin, 10 μM thiorphan and various doses of the putative tachykinin antagonists. Incubations are performed at room temperature for 90 min (NK<sub>1</sub> receptor assays) or 2 hr (NK<sub>2</sub> receptor assay); binding is terminated by addition of 50 mM Tris-HCl buffer (pH 7.4, 4°C) and filtration under vacuum through GF/B filters presoaked with 0.1% polyethyleneimine (NK<sub>1</sub> receptor assays) or 0.5% bovine serum albumin (NK<sub>2</sub> receptor assay). Filter bound radioactivity is quantitated in a gamma counter. Nonspecific binding is defined as binding in the presence of 1 μM substance P or neurokinin A. Specific binding is calculated by subtracting nonspecific binding from total binding. Competition of iodinated SP or NKA binding by test compounds or standards is expressed as a percentage of this maximum competition. IC<sub>50</sub> values (concentration required to inhibit 50% of receptor binding) are generated for each of the test compounds by nonlinear regression using an iterative curve fitting program (GraphPAD Inplot, San Diego, CA).

One skilled in the art can also determine the NK<sub>1</sub> receptor and NK<sub>2</sub> receptor antagonism *in vitro* as follows. Tachykinin-mediated phosphatidylinositol (PI, inositol phosphate) accumulation is measured in UCL1 or SKLKB82#3

-89-

cells in the presence and absence of NK<sub>1</sub> or NK<sub>2</sub> receptor antagonists, respectively. Cells are seeded onto 24 well plates at 125,000 cells/well, two or three days prior to the assay. Cells are loaded with 0.5 mL of 0.2  $\mu$ M myo[2-<sup>3</sup>H(N)]inositol 20-24 hours prior to assay. Cultured cells are maintained at 37°C in a 95% O<sub>2</sub> - 5% CO<sub>2</sub> environment. On the day of the assay, media is aspirated and the cells are incubated in RPMI-1640 medium (for UCL1 cells) or D-MEM/F12 medium (for SKLKB82#3 cells) (containing 40  $\mu$ g/ml bacitracin, 4  $\mu$ g/ml each of leupeptin and chymostatin, 0.1% bovine serum albumin and 10  $\mu$ M thiorphan and 10 mM LiCl) including the test compound is added. After 15 min, SP is added to UCL1 cells or NKA to SKLKB82#3 cells at various concentrations to start the reaction. After incubation for 60 min at room temperature the reaction is terminated by removal of medium and addition of 0.1 mL of methanol to all wells. Two aliquots of methanol (0.5 mL) are added to wells to harvest cells followed by chloroform (1 mL) then doubly distilled water (0.5 mL). Samples are vortexed, centrifuged, and 0.9 ml of the aqueous (top) phase removed and added to 2 ml doubly distilled H<sub>2</sub>O. The mixture is vortexed and loaded onto a 50% Bio-Rad AG 1-X8 (formate form, 100-200 mesh) exchange column (Bio-Rad Laboratories, Hercules, CA). The columns are washed, in order, with: 1) 10 ml doubly distilled water, 2) 5 ml of 5 mM disodium tetraborate/60 mM sodium formate, and 3) 5 ml of 1 M ammonium formate/0.1 M formic acid. The third elution is collected and 1 ml counted in 7 ml scintillation fluid. A 50  $\mu$ l aliquot of the organic (bottom) phase is removed, dried in a scintillation vial and counted in 7 ml scintillation fluid.

The ratio of DPM in the aqueous phase aliquot (total inositol phosphates) to the DPM in the 50  $\mu$ l organic phase aliquot (total [<sup>3</sup>H]inositol incorporated) is calculated for each sample. Data are expressed as a percent of agonist-induced accumulation of [<sup>3</sup>H]-inositol phosphates over basal

-90-

1 vels. The ratios in the presence of test compound  
and/or standards are compared to the ratios for control  
samples (i.e. no stimulating agonist). Dose-response  
graphs are constructed and the ability of the test  
5 compounds to inhibit tachykinin-induced  
phosphatidylinositol turnover determined with the aid of a  
computer program. Data is expressed as percent  
stimulation of total inositol phosphate accumulation over  
basal levels and normalized to the maximum response  
10 produced by SP. Schild analysis is performed using dose  
response curves to obtain a value indicative of the  
strength of a competitive antagonist and is expressed as  
the  $PA_2$ , which is the negative logarithm of the molar  
concentration of antagonist which reduces the effect of a  
15 dose of agonist to one-half of that expected at the dose  
of agonist.

One skilled in the art can determine that the compounds  
of the present invention are  $NK_1$  receptor antagonists *in vivo*  
20 by evaluating the compound's ability to inhibit SP-induced  
plasma protein extravasation in guinea pig trachea. SP-  
induced protein leakage through postcapillary venules is  
assessed by measuring agonist induced Evans Blue dye  
accumulation in guinea pig trachea. Animals are  
25 anesthetized with pentobarbital then injected with Evans  
Blue dye (20 mg/kg, i.v., prepared in 0.9% NaCl solution).  
One minute after dye administration, the antagonist is  
administered (i.v.) followed by SP (0.3 nmole/kg, i.v.)  
and, after 5 min, excess dye removed from the circulation  
30 by transcardiac perfusion with 50 ml 0.9% NaCl solution.  
The trachea and primary bronchi are removed, blotted dry  
and weighed. Dye quantitation is performed  
spectrophotometrically (620 nm) after extracting tissues  
in formamide for 24 hr at 50°C. Values are subtracted  
35 from background (dye only, no agonist).  $ED_{50}$  (dose of  
compound which inhibits SP-induced plasma protein



-91-

extravasation by 50%) is calculated from linear regression analysis.

One skilled in the art can determine that the compounds of the present invention are NK<sub>2</sub> receptor antagonists *in vivo* by evaluating the compounds ability to inhibit NKA-induced respiratory effects. In addition, both NK<sub>1</sub> and NK<sub>2</sub> antagonism can be evaluated after administration of capsaicin, which is known to release both SP and NKA from airway sensory nerves. Antagonism of NKA and capsaicin induced respiratory effects in conscious guinea pigs is carried out as follows. *In vivo* experiments are performed using male Duncan Hartley guinea pigs (250-350g). Changes in conscious breathing patterns are monitored in four animals simultaneously using modified whole body plethysmography consisting of four small plexiglass boxes each connected to a reference box via Validyne DP 45-16 differential pressure transducers. The 4 boxes are equipped with an air supply line (also used for aerosol delivery) and an exhaust air line. Supply and exhaust lines are of the same length and narrow bore and arise from a common supply chamber and vented to a common exhaust chamber. This system is used to ensure that fluctuations in supply air and atmospheric pressure remain in phase and be eliminated from the net signal by the differential pressure transducers. The analog pressure signals are digitalized via a Data Translation DT2821 A to D board. Data are collected at a rate of 100 samples/second/animal. Each cycle of pressure change is analyzed using the following parameters: rising and falling slope determined between minimum and maximum pressures, the ratio of rising over falling slope, and the magnitude of the change between initial trough pressure and peak cycle pressure. Using these values (and observing the animals) the pressure cycles are characterized into normal breaths, forced exhalations (apparent by abdominal heaving), significant respiratory

-92-

events (SREs; usually coughs, less often sneezes or gasps which are characterized by transient, extremely large pressure increases which are distinguishable from noise) and movement/noise with a PCAT 286 running a System V UNIX operating system. Dyspnea is defined as a significant, sustained increase in plethysmograph pressure which is associated with an observable shift to labored breathing in the animal.

10 During the course of a typical experiment in which airway responsiveness to various bronchoconstricting agents is examined, aerosols are delivered for 19 min (0.33 ml/min) using a DeVilbiss Ultraneb 99 ultrasonic nebulizer and plethysmograph pressure monitored during  
15 this time. Prior to nebulization, 1 min of resting breathing pressure data is collected to establish a baseline pressure. In preliminary experiments, various concentrations of the bronchoconstrictive agents are evaluated and the concentration chosen which maximized the  
20 number of animals exhibiting dyspnea but minimized the severity of the response. Hence, neurokinin A is delivered at a final concentration of 0.05%, and capsaicin, 0.001%. The vehicle for nebulization of all bronchoconstrictive agents is phosphate buffered saline  
25 (pH 7.4) which elicits no respiratory effects itself. Putative tachykinin receptor antagonists are administered (i.v.) 20 min prior to onset of aerosol exposure or orally 1 hour prior to onset of aerosol exposure.

30

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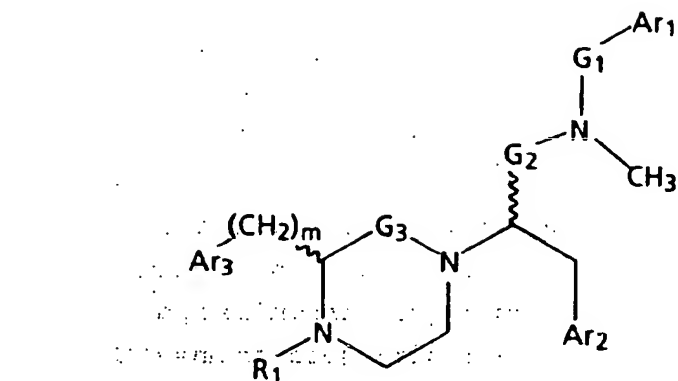
5

WHAT IS CLAIMED IS:

1. A compound of the formula

10

15



20

wherein

G<sub>1</sub> is -CH<sub>2</sub>- or -C(O)-;G<sub>2</sub> is -CH<sub>2</sub>- or -C(O)-;

25

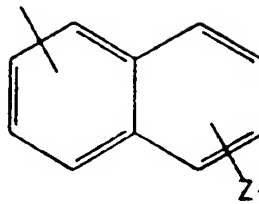
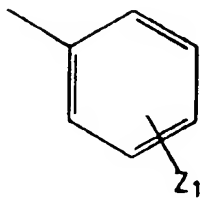
G<sub>3</sub> is -CH<sub>2</sub>- or -C(O)-;

m is 0 or 1;

30

Ar<sub>1</sub> is a radical chosen from the group:

35



wherein

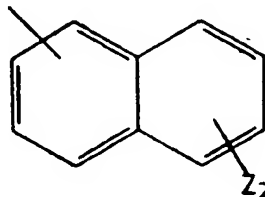
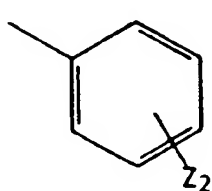
-94-

$Z_1$  is from 1 to 3 substituents each independently chosen from the group consisting of hydrogen, halogen, benzyloxy, hydroxy,  $CF_3$ ,  $C_1$ - $C_4$  alkyl, and  $C_1$ - $C_4$  alkoxy;

5

$Ar_2$  is a radical chosen from the group

10



wherein

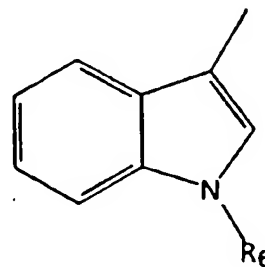
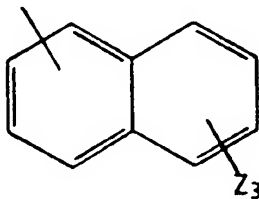
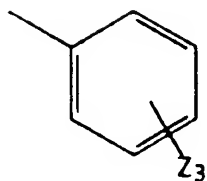
15

$Z_2$  is from 1 to 3 substituents each independently chosen from the group consisting of hydrogen, halogen, benzyloxy, hydroxy,  $CF_3$ ,  $C_1$ - $C_4$  alkyl, and  $C_1$ - $C_4$  alkoxy;

20

$Ar_3$  is a radical chosen from the group

25



wherein

30

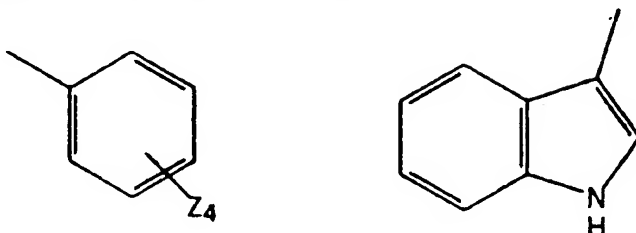
$Z_3$  is from 1 to 3 substituents each independently chosen from the group consisting of hydrogen, halogen, benzyloxy, hydroxy,  $CF_3$ ,  $C_1$ - $C_4$  alkyl, and  $C_1$ - $C_4$  alkoxy;  $R_6$  is hydrogen,  $C_1$ - $C_4$  alkyl, or  $-CHO$ ;

35

-95-

$R_1$  is hydrogen,  $C_1$ - $C_4$  alkyl,  $-(CH_2)_qAr_4$ , or  $-CH_2C(O)Ar_4$  wherein  $q$  is an integer from 1 to 4 and  $Ar_4$  is a radical of the formula

5



10

wherein

$Z_4$  is from 1 to 3 substituents each independently chosen from the group consisting of hydrogen, halogen, benzyloxy, hydroxy,  $CF_3$ ,  $C_1$ - $C_4$  alkyl, and  $C_1$ - $C_4$  alkoxy;

15

or stereoisomers, or pharmaceutically acceptable salt thereof;

20

with the proviso that, when  $G_1$  is  $-C(O)-$ , then  $G_2$  is not  $-C(O)-$ ;

and with the further proviso that, when  $G_3$  is  $-CH_2-$ , then  $G_1$  and  $G_2$  are  $-CH_2-$ .

25

2. A compound of Claim 1 wherein  $R_1$  is hydrogen.

3. A compound of Claim 2 wherein  $G_1$  is  $-CH_2-$  and  $G_2$  is  $-C(O)-$ .

30

4. A compound of Claim 3 wherein  $G_3$  is  $-C(O)-$ .

5. A compound of Claim 1 wherein the compound is (S or R)-2-[(S or R)-3-(1H-indol-3-ylmethyl)-2-oxo-piperazin-1-yl]-1-[N-methyl-N-benzyl-3-(phenyl)-propionamide] or mixtures thereof.

35

-96-

6. A pharmaceutical composition comprising a compound of Claim 1 and a pharmaceutically acceptable carrier.

7. A pharmaceutical composition comprising a compound  
5 of Claim 1 in admixture or otherwise in association with one or more inert carriers.

8. A compound according to Claim 1 for use as a pharmaceutically active compound.  
10

9. A compound according to Claim 8 for the treatment of tachykinin-mediated diseases and conditions.

10. A compound according to Claim 8 for the treatment  
15 of asthma.

11. A compound according to Claim 8 for the treatment of cough.

12. A compound according to Claim 8 for the treatment  
20 of bronchitis.

13. A pharmaceutical composition according to Claim 6 for the treatment of tachykinin-mediated diseases and  
25 conditions.

14. A pharmaceutical composition according to Claim 6 for the treatment of asthma.

15. A pharmaceutical composition according to Claim 6  
30 for the treatment of cough.

16. A pharmaceutical composition according to Claim 6 for the treatment of bronchitis.  
35

17. A method for treating tachykinin-mediated diseases and conditions in a patient in need thereof comprising

-97-

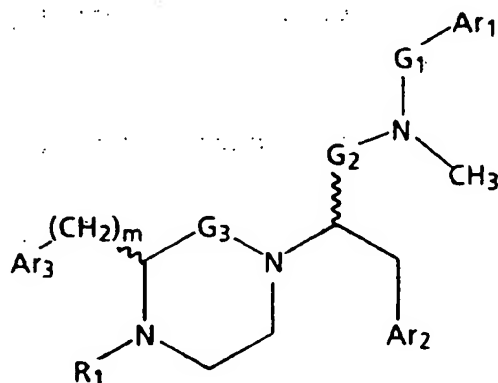
administering to said patient a therapeutically effective amount of a compound of Claim 1.

18. A method for treating asthma in a patient in need thereof comprising administering to said patient a therapeutically effective amount of a compound of Claim 1.

19. A method for treating cough in a patient in need thereof comprising administering to said patient a therapeutically effective amount of a compound of Claim 1.

20. A method for treating bronchitis in a patient in need thereof comprising administering to said patient a therapeutically effective amount of a compound of Claim 1.

21. A process for preparing a compound of the formula



wherein

G<sub>1</sub> is -CH<sub>2</sub>- or -C(O)-;

G<sub>2</sub> is -CH<sub>2</sub>- or -C(O)-;

G<sub>3</sub> is -C(O)-;

m is 0 or 1;

Ar<sub>1</sub> is a radical chosen from the group:

5



10

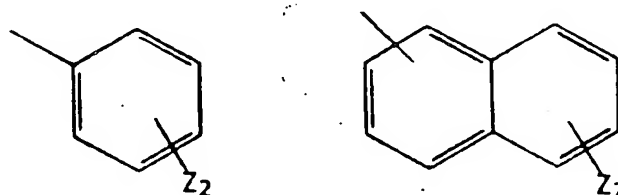
wherein

Z<sub>1</sub> is from 1 to 3 substituents each independently chosen from the group consisting of hydrogen, halogen, benzyloxy, hydroxy, CF<sub>3</sub>, C<sub>1</sub>-C<sub>4</sub> alkyl, and C<sub>1</sub>-C<sub>4</sub> alkoxy;

15

Ar<sub>2</sub> is a radical chosen from the group

20



25

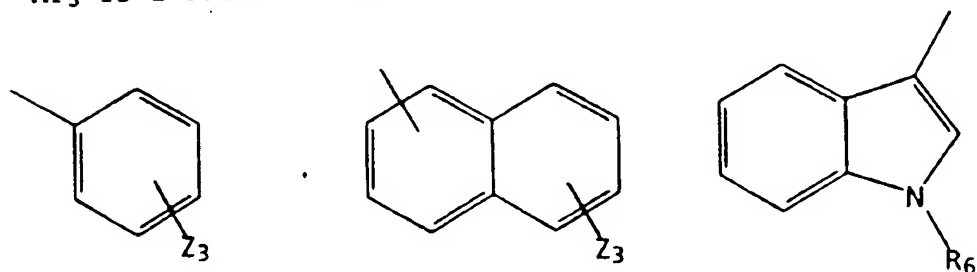
wherein

Z<sub>2</sub> is from 1 to 3 substituents each independently chosen from the group consisting of hydrogen, halogen, benzyloxy, hydroxy, CF<sub>3</sub>, C<sub>1</sub>-C<sub>4</sub> alkyl, and C<sub>1</sub>-C<sub>4</sub> alkoxy;

30

Ar<sub>3</sub> is a radical chosen from the group

35



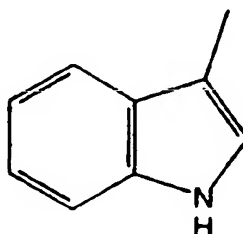
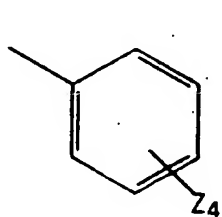


-99-

wherein

$Z_3$  is from 1 to 3 substituents each independently  
chosen from the group consisting of hydrogen,  
halogen, benzyloxy, hydroxy,  $CF_3$ ,  $C_1$ - $C_4$  alkyl, and  
5  $C_1$ - $C_4$  alkoxy;  $R_6$  is hydrogen,  $C_1$ - $C_4$  alkyl, or  $-CHO$ ;

$R_1$  is hydrogen,  $C_1$ - $C_4$  alkyl,  $-(CH_2)_qAr_4$ , or  $-CH_2C(O)Ar_4$   
wherein  $q$  is an integer from 1 to 4 and  $Ar_4$  is a  
10 radical of the formula



wherein

$Z_4$  is from 1 to 3 substituents each independently  
chosen from the group consisting of hydrogen,  
20 halogen, benzyloxy, hydroxy,  $CF_3$ ,  $C_1$ - $C_4$  alkyl, and  
 $C_1$ - $C_4$  alkoxy;

or stereoisomers, or pharmaceutically acceptable salt  
thereof;

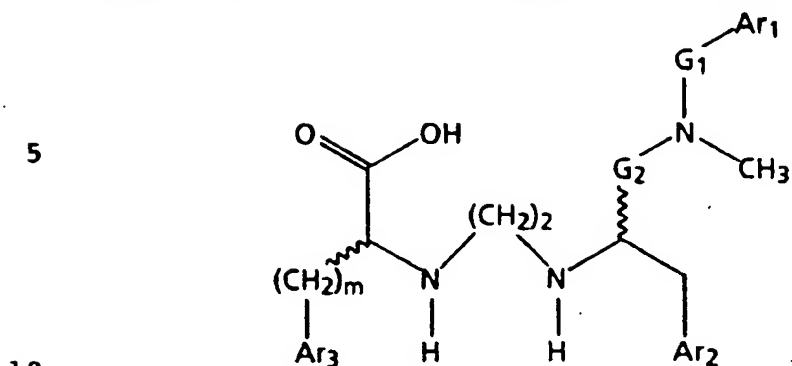
25 with the proviso that, when  $G_1$  is  $-C(O)-$ , then  $G_2$  is not  
 $-C(O)-$ ,

30

35

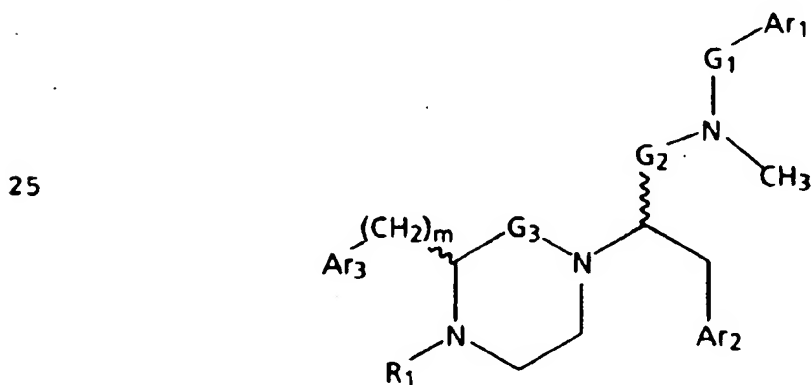
-100-

comprising cyclizing a compound of the formula



wherein  $m$ ,  $G_1$ ,  $G_2$ ,  $Ar_1$ ,  $Ar_2$ , and  $Ar_3$ , are defined above,  
 using a coupling reagent and optionally modifying by  
 alkylation of an amine, an addition reaction to an indole  
 15 nitrogen, or the formation of an amidate and optionally  
 deprotecting and optionally preparing a pharmaceutically  
 acceptable salt by further reacting with an acceptable acid  
 or an acceptable base.

20 22. A process for preparing a compound of the formula



wherein

$G_1$  is  $-CH_2-$  or  $-C(O)-$ ;

35  $G_2$  is  $-CH_2-$  or  $-C(O)-$ ;

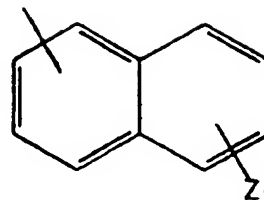
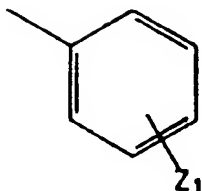
$G_3$  is  $-CH_2-$ ;

-101-

m is 0 or 1;

Ar<sub>1</sub> is a radical chosen from the group:

5



10

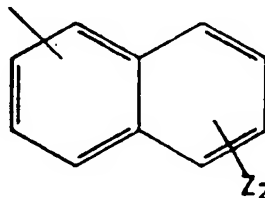
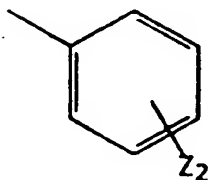
wherein

Z<sub>1</sub> is from 1 to 3 substituents each independently chosen from the group consisting of hydrogen, halogen, benzyloxy, hydroxy, CF<sub>3</sub>, C<sub>1</sub>-C<sub>4</sub> alkyl, and C<sub>1</sub>-C<sub>4</sub> alkoxy;

15

Ar<sub>2</sub> is a radical chosen from the group

20



25

wherein

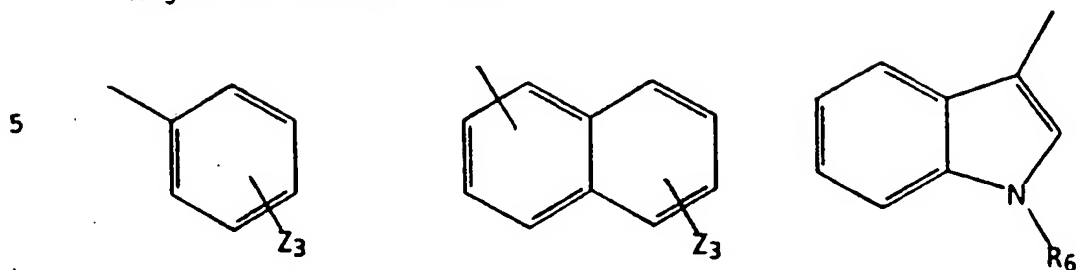
Z<sub>2</sub> is from 1 to 3 substituents each independently chosen from the group consisting of hydrogen, halogen, benzyloxy, hydroxy, CF<sub>3</sub>, C<sub>1</sub>-C<sub>4</sub> alkyl, and C<sub>1</sub>-C<sub>4</sub> alkoxy;

30

35

-102-

$Ar_3$  is a radical chosen from the group



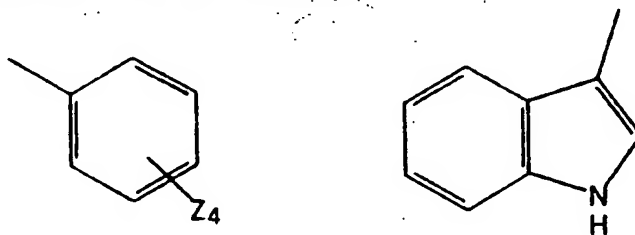
wherein

$Z_3$  is from 1 to 3 substituents each independently chosen from the group consisting of hydrogen, halogen, benzyloxy, hydroxy,  $CF_3$ ,  $C_1$ - $C_4$  alkyl, and  $C_1$ - $C_4$  alkoxy;  $R_6$  is hydrogen,  $C_1$ - $C_4$  alkyl, or  $-CHO$ ;

15

$R_1$  is hydrogen,  $C_1$ - $C_4$  alkyl,  $-(CH_2)_q Ar_4$ , or  $-CH_2C(O)Ar_4$  wherein  $q$  is an integer from 1 to 4 and  $Ar_4$  is a radical of the formula

20



wherein

$Z_4$  is from 1 to 3 substituents each independently chosen from the group consisting of hydrogen, halogen, benzyloxy, hydroxy,  $CF_3$ ,  $C_1$ - $C_4$  alkyl, and  $C_1$ - $C_4$  alkoxy;

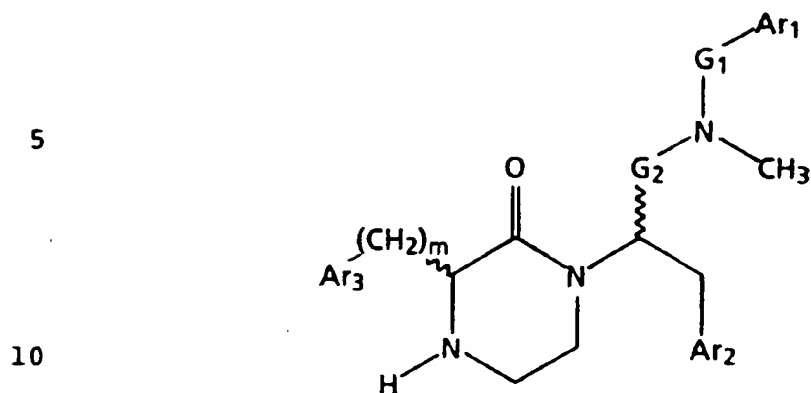
30

or stereoisomers, or pharmaceutically acceptable salt thereof;

35 with the proviso that, when  $G_1$  is  $-C(O)-$ , then  $G_2$  is not  $-C(O)-$ ,

-103-

comprising reducing a compound of the formula



wherein  $m$ ,  $G_1$ ,  $G_2$ ,  $Ar_2$ ,  $Ar_2$ , and  $Ar_3$ , are defined above,  
using amide reducing agent selected from the group  
consisting of lithium aluminum hydride, diisobutylaluminum  
15 hydride, and borane dimethyl sulfide complex and optionally  
modifying by alkylation of an amine, an addition reaction to  
an indole nitrogen, or the formation of an amidate and  
optionally deprotecting and optionally preparing a  
pharmaceutically acceptable salt by further reacting with an  
20 acceptable acid or an acceptable base.

25

30

35

# INTERNATIONAL SEARCH REPORT

Int. onal Application No  
PCT/US 96/02568

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D241/04 C07D241/08 C07D403/04 C07D403/06 C07D403/14  
A61K31/50

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	J. MED. CHEM., vol. 36, 1993, pages 1654-1661, XP002010695 KUCHARCZYK: "Teptrapeptide Tachykinin ..." see page 1655; figure 1	1-22
Y	J. MED. CHEM., vol. 35, 1992, pages 3184-3191, XP002010696 HAGIWARA: "Studies on neurokinin antagonists...." see page 3186; tables II,III	1-22
Y	EP,A,0 333 174 (FUJISAWA PHARMACEUTICAL CO) 20 September 1989 see abstract	1-22
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	-/-	

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

### \* Special categories of cited documents:

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- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- \*a\* document member of the same patent family

Date of the actual completion of the international search

12 August 1996

Date of mailing of the international search report

23.08.96

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Authorized officer

Steendijk, M

# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/US 96/02568

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	GB,A,2 271 774 (MERCK SHARP & DOHME) 27 April 1994 see abstract -----	1-22

# INTERNATIONAL SEARCH REPORT

Information on patent family members

Int. Appl. No.

PCT/US 96/02568

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		AU-B- 3132489	21-09-89
		CA-A- 1329444	10-05-94
		DE-D- 68926403	13-06-96
		JP-A- 1287095	17-11-89
		US-A- 5187156	16-02-93
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GB-A-2271774	27-04-94	NONE	
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